ON HUMAN NATURE

BIOLOGY, PSYCHOLOGY, ETHICS, POLITICS, AND RELIGION

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On Human Nature

Biology, Psychology, Ethics, Politics, and Religion

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Academic Press is an imprint of Elsevier

Academic Press is an imprint of Elsevier
125 London Wall, London EC2Y 5AS, United Kingdom
525 B Street, Suite 1800, San Diego, CA 92101-4495, United States
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom

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Library of Congress Cataloging-in-Publication Data
A catalog record for this book is available from the Library of Congress

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

ISBN: 978-0-12-420190-3

Publisher: Sara Tenney
Acquisition Editor: Kristi Gomez
Editorial Project Manager: Pat Gonzalez
Production Project Manager: Laura Jackson
Designer: Maria Inês Cruz

Typeset by TNQ Books and Journals

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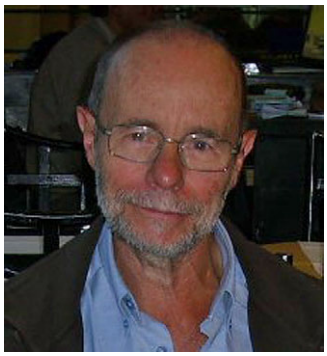
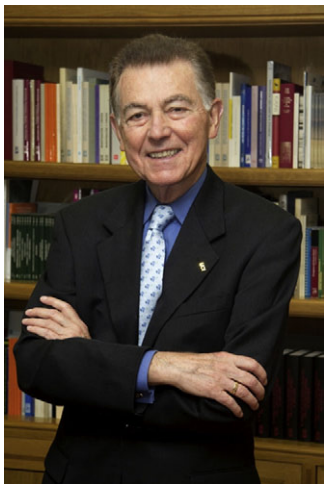


Michel Tibayrenc, MD, PhD, has worked on the evolution of infectious diseases for more than 35 years. He is a director of research emeritus at the French Institut de Recherche pour le Développement (IRD), the founder and editor-in-chief of *Infection, Genetics and Evolution* (Elsevier), with a 2014 impact factor of 3.015, and the founder and principal organizer of the international congresses MEEGID (molecular epidemiology and evolutionary genetics of infectious diseases). He is the author of more than 200 international papers. He has worked for one year in Algeria (as a general practitioner), one year in French Guiana, seven years in Bolivia, five years in the United States, and three years in Thailand. He has been the head of the unit of research "genetics and evolution of infectious diseases" at the IRD research center in Montpellier, France, for 20 years. With his collaborator Jenny Telleria, he is the founder and scientific adviser of the Bolivian Society of Human Genetics (2012). He has won the prize of the Belgian Society of tropical medicine (1985), the medal of the Instituto Oswaldo Cruz, Rio de Janeiro (2000), for his work on Chagas disease, and he is a fellow of the American Association for the Advancement of Science (1993).



Francisco J. Ayala is University Professor and Donald Bren Professor of Biological Sciences and Professor of Philosophy at the University of California, Irvine. On June 12, 2002, President George W. Bush awarded him the 2001 National Medal of Science at the White House. On May 5, 2010, he received the 2010 Templeton Prize for exceptional contribution to affirming life's spiritual dimension from HRH Prince Philip, Duke of Edinburgh, at a private ceremony in Buckingham Palace, London.

Born in Madrid, Spain, he has lived in the United States since 1961, and became a US citizen in 1971. He has published more than 1100 articles and is the author or editor of 50 books, including *Essential Readings in Evolutionary Biology* (2014), *The Big Questions: Evolution* (2012), *Am I a Monkey?* (2010), *Human Evolution* (2007), and *Darwin's Gift to Science and Religion* (2007).

He is a member of the U.S. National Academy of Sciences, the American Academy of Arts and Sciences, and the American Philosophical Society, a Fellow of the Linnean Society of London, Foreign Member of the

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Ayala has received the Gold Honorary Gregor Mendel Medal from the Czech Academy of Sciences, the Gold Medal of the Accademia Nazionale dei Lincei, the Gold Medal of the Stazione Zoologica of Naples, the President's Award of the American Institute of Biological Sciences, the Scientific Freedom and Responsibility Award from the AAAS, the Medal of the College of France, and numerous other recognitions and awards. He has also received honorary degrees from 24 universities in 10 countries.

Foreword

Science has evolved through the centuries by the entanglement of two very different modes of creative inquiry. The first mode is the straightforward discovery of new phenomena, typically made more likely by technological advance. For example, researchers are now able to determine the age of most fossil and archaeological remains by the amount of radioactive decay measured within them. They can track local brain activity with functional magnetic resonance imaging. By shifting to frequencies higher than visible light on the electromagnetic spectrum, they are able to find and study microorganisms too small to be seen with conventional light microscopy. And by discovering "missing link" species by whatever means, the researchers can draw more accurate, and often surprising, evolutionary family trees.

The second mode of inquiry is the synthesis of new and old information across disciplines. Soon after the structure of DNA was adduced, its base-pair code was broken, then linked to the already well-established principles of particulate heredity. There ensued a linkage to the mother lode of established biochemistry and cell architecture. A major consequence was the inauguration of molecular biology, whose achievements suffice to designate the second half of the 20th century as the golden age of modern biology.

As the veils of mystery in biology have been removed one by one, the cause-and-effect explanations have drawn closer together. Hybrid disciplines became the rule in biology, yielding, for example, behavioral ecology, physiological ecology, biochemical physics, developmental biology, economic botany, neurobiology, population genetics, sociobiology, and a thicket of others, each attended by its own journals and well-trained experts.

At first thought this proliferation of specialties may seem a symptom of the splintering of biological knowledge. But the opposite is true. The hybrid disciplines are better recognized as silos that researchers have built to master detailed information and thereby to promote original discoveries. When biology is viewed as a whole, the principles, the fundamentals, and even the styles of expression are seen as actually convergent. The overall network of biological knowledge it expresses is tightening. One result is the production of ever farther-reaching syntheses such as the one presented in this book, which dares to take biology deeper into the humanities, and the humanities deeper into biology.

The contribution of the present work, *On Human Nature: Biology, Psychology, Ethics, Politics, and Religion*, is potentially profound. It is encyclopedic in coverage, written by leaders in a large part of human biology rarely covered within a single volume. Its aim, according to the editors, is to evaluate "the present state of knowledge on human diversity and its adaptive significance through a broad selection of representative chapters." Its center is the crossroads between biology and the human sciences.

On Human Nature uses detailed information to disclose how and when humanity originated, what we are today, and why we behave the way we do in an increasingly fragile world of our own making. The content is fearless, tracking change not just through the dawn of history in Neolithic times, but much deeper into Paleolithic times, when our physiological and emotional responses were programmed by genetic evolution.

From the same perspective it is entirely appropriate for some of the authors in the symposium, as elsewhere among many scholars, to carry biological reasoning into subjects traditionally reserved for the humanities. It has become increasingly evident—although far from conclusively proven—that the biological sciences are not separated from humanistic explanations of aesthetics and moral reasoning, at least not by the divide of seismic proportions formerly accepted. Like other traits of physiology and behavior, they are guided by emotional responses programmed from the start by genetic evolution. "Human nature" is a concept appropriately applied to characterize traits of this bedrock origin. Biological research is the truest way to track its influence, or lack of influence, during the evolutionary transition from instinct to culture.

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Preface

The late Nobel Prize winner Jacques Monod used to say that the ultimate goal of science was to elucidate Human Nature. Monod, a molecular biologist, had written the famous book *Chance and Necessity*, which expressed a striking neodarwinian, reductionist, and atheist view of the living world. The properties of the genetic code, recently discovered at that time (the book was published in 1970) appeared to Monod as evidence that absolute chance was at the root of evolution. It was not a hypothesis: it was a certainty. For the author, blind natural selection ("Necessity") was able to fully explain teleonomy (the obvious purposefulness of living organisms' features).

We now know much more genetics and biology than Monod did. However, to the eyes of many, genetics and evolutionary studies are far from being able to provide a comprehensive and sophisticated view of human nature. These studies only bring some important parts of the puzzle, while many questions remain unanswered. This is also the thinking of the two editors and initiators of this book. This is why, when designing the project, we decided to cover as broad a range as possible of all fields of knowledge that would enlighten human nature. Controversies are neither avoided nor hidden. However, subjects that, in the view of the editors—rightly or wrongly asserting their decision—do not meet the requirements of methodological rigor (such as creationism and intelligent design) were not included in the project. Otherwise, the book presents a fair balance between social, medical, and biological sciences. Authors were asked to make their chapters accessible to a broad range of readers, including students, teachers, and the educated public. However, all chapters are quite up to date and include all recent advances in their field, which should make them highly relevant to specialists as well.

The book comprises three parts, intended to be complementary to each other and purposely featuring some overlap and redundancy:

Part I: Biological Basis of Human Diversity

Part II: Psychology, Behavior and Society

Part III: Ethics, Politics and Religious Considerations

The editors decided that each author would deliver her/his chapter independently from other authors. Authors were aware about the whole design and content of the book, and of the identity of other authors. However, they did not read the other chapters of the book. Authors were only given a few basic indications about the concept of the book. Chapters were reviewed by the editors only, who interfered as little as possible with the final outcome. The goal of this way of processing was to get the personal vision of each author about her/his own field. The whole design and set of chapters has been extensively discussed between the two editors, as well as the selection of authors. The topics were selected before identifying authors. Once a topic was agreed on between the two editors, top authors were selected either from personal contacts or through relevant databases. The selection of topics is a reflection of how the editors conceive what should not be a full synthesis about human nature but rather a diversified sample of how human intelligence approaches various facets of human nature. Selection of topics and authors certainly is not beyond criticism. Moreover, the two editors are both Westerners and trained in the tradition of modern biology. A book on human nature designed by Thai Buddhist monks or Amazonian forest native shamans would certainly have been quite different—and fascinating. Cultural and professional biases as well as ethnocentrism are sins shared by everyone on Earth. Nevertheless, the design of the book should be considered to be free of any deliberate bias or thematic imperialism.

Michel Tibayrenc
Francisco J. Ayala

Part I

Biological Basis of Human Diversity

Chapter 1

The Advent of Biological Evolution and Humankind: Chance or Necessity?

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CHANCE AND NECESSITY

Chance and Necessity is the title of a book written by Jacques Monod which explains how DNA is expressed in the enzymes and proteins determining the organism's phenotype. Monod holds that "[t]he initial elementary events which open the way to evolution in the intensely conservative systems called living beings are microscopic, fortuitous, and totally unrelated to whatever may be their effects upon teleonomic functioning" (Monod, 1970, 1971, p. 114). More than four decades later, we keep in mind the same view: evolution starts fortuitously, and unrelated to effects or events. These microscopic events mean "novelties" that, as Monod said, "in the shape of an alteration of the protein structure, will be tested before all else for its compatibility with the whole of the system already bound by the innumerable controls commanding the execution of the organism's projective purpose" (Monod, 1971, p. 115).

The word "purpose" obviously is polysemic, meaning desires, ends, goals, determinations, resoluteness, and designs, but also meaning practical results. The teleonomic functioning that is affected by the initial, fortuitous events could be explained in any of these several levels of "purpose." Environment also counts: "Let us say that the 'initial conditions' of selection encountered by a new mutation simultaneously and inseparably include both the environment surrounding it and the total structures and performances of the teleonomic apparatus belonging to it." (Monod, 1971, p. 121). In the end, "It is obvious that the part played by teleonomic performances in the orientation of selection becomes greater and greater, the higher the level of organization and hence *autonomy* (Monod's emphasis) of the organism with respect to its environment—to the point where teleonomic performance may indeed be considered decisive in the higher organisms, whose survival and reproduction depend above all upon their behavior." (Monod, 1971, p. 121).

The *necessity* expressed by the organism's purposes may seem to lead us to a Lamarckian-like scheme. However, "teleonomy" and "purpose" are related, in Monod's analysis of the whole process of evolution, to the results of every organism's fight for survival and reproduction. A true Lamarckian scheme should relate the teleonomic purpose to the reproduction, ie, transmission of the organism's achievements in its fight for survival. Is this the case?

Monod's work is an example of an anti-Lamarckian interpretation of the links existing between proteins and nucleic acids. With his own words "there is no *possible* (Monod's emphasis) mechanism whereby the structure and performance of a protein could be modified, and these modifications transmitted even partially to posterity, except an alteration of the instructions represented by a segment of DNA sequence" (Monod, 1971, p. 107−108).

However, the lack of a mechanism for transmitting protein modifications to the DNA does not preclude the existence of other kind of heredity linked not to the genetic material but to its development. This is the case of epigenetic processes.

EPIGENETIC PROCESSES

We will take epigenetics as the "DNA sequence-independent changes in chromosomal function that yield a stable and heritable phenotype" (Rissman and Adli, 2014). The phenotype may refer to the whole organism, or to only particular cells or tissues. Three conditions must be fulfilled for an epigenetic process, currently called transgenerational epigenetic inheritance (TEI): (1) changes in

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00001-6

chromosomal function expressed in a different phenotype (different from parents' phenotype); (2) independent from DNA sequences (neither coded in the genome, nor linked to parents' germ cells alterations—see Choi and Mango, 2014); (3) which is heritable in a stable way (persisting for at least three generations). As Choi and Mango say, "Both invertebrates and vertebrates exhibit such inheritance, and a range of environmental factors can act as a trigger." The challenge is to ascertain "what molecular mechanisms account for inheritance of TEI phenotypes" (Choi and Mango, 2014).

Mechanisms leading to TEI have been related to (see Rissman and Adli, 2014):

- DNA methylation (a biochemical process in which methyl chemical groups are covalently attached to cytosine residues by DNA methyltransferase enzymes);
- histone modifications (posttranslational modifications in histone proteins, mainly studied in organisms, such as *Caenorhabditis elegans*, lacking DNA methylation);
- ncRNAs (noncoding RNA that alters chromatin structure and DNA accessibility).

The need for these mechanisms seems clear. Though all cells share a common nuclear genome, the necessity for genetic expression, from DNA to proteins, varies in the different tissues. Thus, a great part of the genome must be silenced, not leading to codify any protein or enzyme. This silencing strategy is reached during the ontogenetic development, ie, by means of epigenetic episodes. Several factors, including environmental conditions and parental care, seem to affect epigenetics. If the alterations provoked are inherited, we are facing a TEI phenotype.

Chance has a great role in the phylogenetic appearance of any new organism. As we know, paleontology is a historical science: it does not consist of predictive laws. Rather, it describes the evolutionary changes that occurred in evolution. These changes include processes such as mutation, genetic recombination ensuing from sexual reproduction, and epigenetic events prompted by particular environmental circumstances. What about necessity? It is imposed by the environmental circumstances associated with each evolutionary episode. Every population of organisms must remain adapted to the demands of its ecosystem or it will lose its biological fitness.

Epigenetic processes become a kind of intermediate expanse between absolute chance—the fortuitous modification of DNA—and required necessity—the suitability of new proteins to adapt to environment. Epigenetics have been used sometimes as an argument against the neo-Darwinist approach to evolution. The fact that noncoding changes could be inherited has been claimed as something like a Lamarckian approach. However, no mysterious process that might be achieved by an organism's alleged "will" exists. DNA silencing obviously depends on genetic information appearing by means of well-known molecular mechanisms. All TEI phenotypes are the result of genetic, inheritable material that, under external—environmental, at least relative to the cell or tissue—pressures, becomes modified. TEI phenotypes are inherited because parents transmit not only DNA to the progeny but also because the mother contributes with a whole set of cellular organs, as well as several kinds of ncRNA, included in the ovule.

This chapter will engage these two components, hazard and necessity, of human evolution, exploring how they participate and become integrated in the human phylogeny.

WHAT IS A HOMININ?

We humans form an evolutionary lineage among those belonging to the order Primata. According to the traditional classification, the order Primata includes three suborders (Anthropoidea, Tarsioidea, and Prosimii). The suborder Anthropoidea includes two infraorders, Catarrhini (African, European, and Asian monkeys) and Platyrrhini (American monkeys), which diverged after continental drift separated South America from Africa. Catarrhini are divided into two superfamilies: Cercopithecoidea (Old World monkeys) and Hominoidea (apes and humans; hominoids in popular terms; see Table 1.1).

In the 1960s, with analyses of proteins in the blood serum of hominoids, Morris Goodman, a molecular geneticist at Wayne State University in Detroit, determined that humans, chimpanzees, and gorillas are closer to each other than any of them is to orangutans (Goodman, 1962, 1963; Goodman et al., 1960). According to Goodman's results the evolution of hominoids proceeded very differently from what Simpson's taxonomy implied. The lineage leading to orangutans was the first to split, then the lineage of gorillas split from the others, and, finally, the chimpanzees and human lineages diverged from each other. Consequently, using the language of cladistics, lineages of humans and chimpanzees are "sister groups." They come from a common ancestor and thus share remarkable similarities. Regarding the age of the split of these sister groups, Vince Sarich and Alan Wilson (1967a,b) argued that the rate of genetic change in chimpanzees and humans was fast, and estimated that the divergence of the evolutionary branches of the last two hominoid lineages took place 4–5 Ma (mega-annum, million years) ago.

Here we will adopt a taxonomic classification which respects the increasing molecular evidence. We will largely follow Bernard Wood and Brian Richmond (2000; Table 1.1). The family Hominidae embraces the set of great apes and humans. Orangutans constitute the subfamily Ponginae and gorillas the subfamily Gorillinae, while chimpanzees and humans form the subfamily Homininae. Within the latter, chimpanzees belong to the tribe Panini and humans to the tribe Hominini. The human lineage has

TABLE 1.1 The Suprageneric Taxonomy of Great Apes and Humans

Family	Subfamily	Tribe	Subtribe	Current Species
Hominidae	Ponginae	Pongini	Pongina	Orangutans
	Gorillinae	Gorillini	Gorillina	Gorillas
	Homininae	Panini	Panina	Common chimpanzees; bonobos
		Hominini (hominins)	Ardipithecina (ardipiths) Australopithecina (australopiths) Paranthropitecina (robusts australopiths) Hominina (hominans or, for short, homo)	Humans

In brackets, popular names.
Adapted from Wood, B., Richmond, B.G., 2000. Human evolution: taxonomy and paleobiology. Journal of Anatomy 196, 19–60, adding the subtribes Ardipithecina and Paranthropitecina.

the category of tribe: Hominini (informal name, "hominins"). Two subtribes are included in it. One is Australopithecina (informal name "australopiths"), which encompasses four genera: *Orrorin, Ardipithecus, Australopithecus, Paranthropus*. The other subtribe is Hominina (informal name, "hominina", or just "homo"), with one single genus, *Homo*.

Our interest is focused on the tribe Hominini, which defines current humans and some of our extinct ancestors as a distinct group; it does not include our closest living relatives. The question of whether hominin and African ape clades constitute tribes, as we support, or families, subfamilies, or even genera, is irrelevant to the present discussion. It does not alter the basic question regarding the relative distribution of lineages.

The term "hominin" is extensively used in the scientific literature to identify members of the human lineage, ie, direct and collateral ancestors that are not also ancestors of other living hominoids, though it has not yet been widely adopted in popular writings.

HUMAN SIMILARITIES AND DIFFERENCES

Apart from taxonomy, what a hominin is can be inferred from genetic and phenotypic comparison between humans and modern chimpanzees. DNA hybridization studies (Sibley and Ahlquist, 1984) have shown that chimpanzees and humans share close to 98% or 99% of their genomic DNA. The direct sequencing of the human chromosome 21(Hattori et al., 2000) and its orthologue 22 in chimpanzees (Watanabe et al., 2004) allowed the detailed comparison of their genomes, confirming their genetic proximity. Excluding deletions and insertions, the differences between the two species amounted to only 1.44% of the nucleotides. It became obvious that the genomes of humans and chimpanzees are extremely similar in their DNA sequence. How similar has become recently known with the publication of the draft genome sequence of the chimpanzee and its preliminary comparison to the human genome.

The Human Genome Project of the United States was initiated in 1989 and funded through two agencies, the National Institutes of Health (NIH) and the Department of Energy (DOE) with eventual participation of scientists outside the United States. A draft of the genome sequence was completed ahead of schedule in 2001 (International Human Genome Sequencing Consortium, 2001). In 2003 the Human Genome Project was finished, but the analysis of the DNA sequences chromosome by chromosome continued over the following years. Results of these detailed analyses were published on June 1, 2006, by the Nature Publishing Group, in a special supplement entitled *Nature Collections: Human Genome*.

The draft DNA sequence of the chimpanzee genome was published on September 1, 2005, by the Chimpanzee Sequencing and Analysis Consortium (2005) embedded within a series of articles and commentaries called *The Chimpanzee Genome*. The last paper in the collection presents the first fossil chimpanzee ever discovered (McBrearty and Jablonski, 2005).

In the genome regions shared by humans and chimpanzees, the two species are 99% identical. These differences may seem very small or quite large, depending on how one chooses to look at them: 1% of the total appears to be very little, but it amounts to a difference of 30 million DNA nucleotides out of the 3 billion in each genome. Twenty-nine percent of the enzymes and other proteins encoded by the genes are identical in both species. Out of the one hundred to several hundred amino acids that make up each protein, the 71% of nonidentical proteins differ between humans and chimpanzees by only two amino acids, on average. If one takes into account DNA stretches

found in one species but not the other, the two genomes are about 96% identical, rather than nearly 99% identical as in the case of DNA sequences shared by both species. That is, a large amount of genetic material, about 3% or some 90 million DNA nucleotides, have been inserted or deleted since humans and chimps initiated their separate evolutionary ways, about 6−8 Ma ago. Most of this DNA does not contain genes coding for proteins, although it may include tool-kit genes and switch genes that impact developmental processes, as the rest of the noncoding DNA surely does.

Comparison of the two genomes provides insights into the rate of evolution of particular genes in the two species. One significant finding is that genes active in the brain have changed more in the human lineage than in the chimp lineage (Khaitovich et al., 2005). Also significant is that the fastest evolving human genes are those coding for "transcription factors." These are "switch" proteins, which control the expression of other genes, that is, they determine when other genes are turned on and off. On the whole, 585 genes have been identified as evolving faster in humans than in chimps, including genes involved in resistance to malaria and tuberculosis. (It might be mentioned that malaria is a severe disease for humans but not for chimps.) There are several regions of the human genome that contain beneficial genes that have rapidly evolved within the past 250,000 years. One region contains the *FOXP2* gene, involved in the evolution of speech.

Other regions that show a higher rate of evolution in humans than in chimpanzees and other animals include 49 segments, dubbed human accelerated regions (HARs). The greatest observed difference occurs in *HAR1F*, an RNA gene that "is expressed specifically in Cajal-Retzius neurons in the developing human neocortex from 7 to 19 gestational weeks, a crucial period for cortical neuron specification and migration" (Pollard et al., 2006; see also Smith, 2006).

All this knowledge (and much more of the same kind that will be forthcoming) is of great interest, but what we so far know advances but very little our understanding of what genetic changes make us distinctively human. Extended comparisons of the human and chimpanzee genomes and experimental exploration of the functions associated with significant genes will surely advance further our understanding, over the next decade or two, of what it is that makes us humans, what it is that differentiates *Homo sapiens* from our closest living species, chimpanzees and bonobos, and will provide some light on how and when these differences may have come about during hominid evolution.

The comparative studies also lead to an initially surprising conclusion: although genome differences are very tiny, differences between the resulting proteins are not. Most of the proteins coded by chromosomes 21/22 are different in humans and chimpanzees. The estimate calculated by Galina Glazko et al. (2005) places the difference close to 80%, which naturally leads to the differences between the phenotypes of *Homo* and *Pan*.

How can this fact be interpreted in evolutionary terms? As Maryellen Ruvolo (2004) said in this regard, when genomes of more distant species such as humans and mice are compared, the basic premise is "if it's conserved, it must be functionally important." By contrast, for closely related species, such as humans and chimpanzees, the basic premise is "if it's different, it might be important in explaining species differences." Let us proceed, then, with an attempt to understand the reasons for the differences in this case.

The discrepancy between small molecular distance and large protein distance is explained by gene expression, by the way in which information contained in the genome leads to a protein. It is clear that genome expression is not equivalent in chimpanzees and humans. But the genome itself also contains some notable differences that are not expressed in genetic distance when compared sequence by sequence. The human genome is comparatively larger than that of chimpanzees and other primates like lemurs because of a greater number of insertions. To give an example, the human *Alu* gene has experienced twice the number of insertions as its corresponding gene in chimpanzees during the separate evolution of both lineages (Hedges et al., 2004). Chromosomes of each lineage have also suffered rearrangements, which have been related with encoding different proteins (Navarro and Barton, 2003), although a later, larger study denied that relationship (Vallender and Lahn, 2004). In any case, the basic issue in evolutionary terms is, as mentioned, to identify which expression regions of genes carry functional differences—that is, what particular differences are involved in producing a human or chimpanzee, starting from a fairly similar DNA.

Much of the difference between the two sibling groups, from locomotion to the way they communicate, is functional; ultimately, to some extent dependent on those protein functions to which Ruvolo (2004) referred when talking about the evolutionary significance of disparities obtained, either by molecular transformations, positive selection of protein changes, or differential gene expression. But identifying genetic differences that translate into functional differences in either lineage is, for the moment, beyond our capacity. The available panorama is very poor; for instance, only one gene related to language production, *FOXP2*, is known, and its peculiarities appear to be the result of a mutation that occurred after the human lineage separated from the chimpanzee (Enard et al., 2002). However, *FOXP2* is related to motor control disorders that hinder language, not to the act of speaking (Cela-Conde

et al., 2008). Perhaps the strongest evidence for a genetic, anatomical, and functional correlate would be the mutations suffered in the Myosin gene of *Homo* (Stedman et al., 2004), which would have allowed the development of large crania in our genus. The possible role of this gene has also been discussed (Perry et al., 2005).

THE DISTINCTIVE FEATURES OF HUMANS

Technically, "apomorphy" is a distinctive feature of a lineage that is not found in the sibling group, and forms, therefore, a distinguishing characteristic.

Sean Carroll (2003), in his study of the genetic basis of the physical and behavioral traits that distinguish humans from other primates, gave a list of distinctive human apomorphies:

- Body shape and thorax
- Cranial features (brain case and face)
- Brain size
- Brain morphology
- Limb length
- Long ontogeny and lifespan
- Small canine teeth
- Skull balanced upright on vertebral column
- Reduced hair cover
- Elongated thumb and shortened fingers
- Dimensions of the pelvis
- Presence of a chin
- S-shaped spine
- Language
- Advanced tool making.

Some of the apomorphies listed by Carroll are functional, like language. Others that are anatomical are not shown in fossils, like hair or the brain's topology. However, body shape, brain size, relative length of limbs, and vertically placed cranium above the vertebral column are morphological traits that clearly set us apart from any ape. Moreover, many distinctive human traits have appeared recently; if we look back in time they disappear from our lineage. Ten thousand years ago neither writing nor agriculture existed. Fifty thousand years ago there were no people in America. These are negligible time intervals relative to the several million years that have passed by since the divergence of the evolutionary branches leading to the African great apes and humans.

Thus, current human features are generally not very helpful to reach conclusions about our initial apomorphies. What we are looking for are derived ancient traits that can be considered synapomorphic, shared by every hominin that ever existed. These would define the earliest member of our lineage as adaptively distinct. Leaving aside the necessarily dark period surrounding the exact moment when the lineages split, are there any such traits? Can we find a trait that will allow us to determine whether a given fossil specimen is a hominin?

It is generally accepted nowadays that bipedalism is a hominin synapomorphy—an apomorphy shared by all the members of the lineage. Thus, being a primate bipedal equals being a hominin. Any specimen close to the divergence between the chimpanzee and human lineages is attributed to the latter if it is bipedal. Most of the modifications to the trunk, limbs, hip, and the insertion of the vertebral column in the skull are related to bipedalism, which distinguishes our species from the apes. Since bipedal specimen with ages around 6–7 Ma have been found in Chad (Brunet et al., 2002), Kenya (Senut et al., 2001), and Ethiopia (White et al., 2009), we may take the Late Miocene as the epoch in which the split between chimpanzees and humans took place.

CHANCE AND NECESSITY IN HUMAN EVOLUTION

Let us summarize what we have presented, thus far. The hominin lineage appeared about 7 million years ago in the tropical forests of the Rift depression, associated with an essential apomorphy: bipedal locomotion that separated humans from chimpanzees. In time, the human lineage diversified and dispersed, colonizing the whole planet.

The different clades of the human lineage gradually developed adaptive specializations. One of its branches, the genus *Homo*, managed to live until the present. Coming back to the title of this chapter, would this journey express just hazardous episodes that modulated the evolutionary development of the human lineage? Or was the acquisition of our current traits—be they bipedalism or the kind of apomorphies typical of *Homo*, including language, morals, aesthetics, and sophisticated technology—somehow necessary?

According to the roles that we have given to chance and necessity, following the argument of Monod, one quickly concludes that both components are involved when any trait is fixed. Evolution involves, first, the need for (random) changes to appear in the genetic material, which often affect epigenetic events whose relationship with the environment is very close. In that way, the imposed necessity to adapt to any ecosystem becomes the other side of the coin in a complex process. The issue is to determine to what extent genetic and environmental components influence the appearance of a particular trait.

Can we indicate with which genetic changes bipedalism is related, and what adaptive advantages it provides in the ecosystem of the first hominids? The first question has necessarily a negative answer at this time. The genetic

components of Miocene hominids are completely unknown. The alternative chance/necessity could be transferred, however, to the field of adaptation. If it is possible to identify clear adaptive advantages in bipedalism, then the component of necessity gains relevance. If we find it difficult, or even impossible, to associate bipedalism to adaptive advantages, the component of chance gains weight.

Darwin envisioned the following chain of events regarding human evolution: descent from the trees, bipedalism, brain size increase, language, and appearance of culture (with all its components, both intellectual and technological). Some of these elements can be traced in the fossil record, but not others. Phenomena such as the development of moral sense, which Darwin believed was extremely important, are not associated with fossil remains. Language does not fossilize either. But the cranium and bones of the hip and lower limbs leave fossil trails that can provide firm evidence regarding whether it was our bipedal posture or our large brain that developed first.

During the early 20th century there were defenders of two opposite hypotheses. Arthur Keith was one of the most notorious advocates for bipedalism as the initial trait, while Grafton Elliot Smith argued that a large encephalization appeared first. The swords were drawn when the Piltdown fossil specimen appeared on the scene. The specimen had a large cranium, the size of the cranium of a modern human, combined with a very primitive mandible, resembling that of an orangutan or gorilla. The different fragments that formed the specimen were found in 1912 by Charles Dawson, an amateur archaeologist in the English town of Piltdown. The story of its discovery and the controversy it sparked has been told many times. The article that *The London Illustrated News* devoted to the finding in September 1913 renders a very good picture of the challenges posed by the specimen's interpretation (Pycraft, 1913).

The Piltdown fossil exhibited some unconvincing traits, such as the awkward connection between the cranium and mandible—raising the suspicion that they belonged to different specimens. Many paleontologists were indeed suspicious. Its discoverers did not allow its examination, alluding to the fragility of the original fossil. It was necessary to use copies made with a mold. The suspicions turned out to be well founded. In 1953 (thanks to Joseph Weiner, Kenneth Oakley, and Wilfred Le Gros Clark) it was confirmed that the Piltdown fossil was a fraud. Someone had filed an orangutan's mandible and canines to reduce them and fit them, quite sloppily, to a human cranium. The main suspect of the fraud is Martin Hinton, curator of the Natural History Museum, London. Hinton was the owner of a trunk found in the museum's attic in 1996, with bones manipulated in a similar way to those constituting the Piltdown specimen (Gee, 1996).

Before the Piltdown deception, there already was evidence contrary to the early evolution of a large brain. Remains of fossil beings that were very similar to us were known since the beginning of the 19th century, before the controversy between evolutionists and antievolutionists reached the virulence sparked by Darwin's work. The discovery of a very famous specimen in 1856, the Neander valley cranium (Germany), which would christen the Neandertals, occurred several years before the publication of Darwin's *Origin of Species*. But the first "modern" discoveries, that is to say, interpreted in terms of evolutionary ideas, were made after 1887, subsequent to the arrival of the Dutch physician Eugène Dubois in Indonesia. As a hobby, Dubois searched for fossils that could prove Darwin was right. At the Javanese site of Trinil, Dubois discovered in 1891 remains that completely transcended the realm of scientists and became universally known. The specimen includes a primitive and small cranium (with a capacity of about 850 cc) found beside a femur that was very similar to that of modern humans. The name given to the taxon, *Pithecanthropus erectus*, means upright ape-man, conveying the idea that it was an intermediate being between humans and apes (*pithecus* for ape, and *anthropus* for human); and that it had a posture distinctively upright (*erectus*) (Dubois, 1894). Eugène Dubois gave to the fossil a very different significance from the one we give it today (Dubois, 1894). For Dubois, *Pithecanthropus* was a gigantic genus of the gibbon's type, although superior because of their large brains and ability to assume an erect posture (Dubois, 1935). The fact that Lydekker had discovered *Paleopithecus sivalensis*, ancestor of the gibbon, in Siwaliks (Pakistan) in 1879, must have influenced this diagnosis.

Subsequent discoveries have required revising Dubois' interpretations. The Trinil fossil is not an "intermediate" form between humans and apes, but a fairly advanced hominin. The upright posture was not a new apomorphy; rather it was already present in its ancestors. But Dubois' phylogenetic interpretation was correct: the ancestors of current humans had fixed a bipedalism similar to our own before the brain reached its current size.

CAN ADAPTIVE ADVANTAGES OF BIPEDALISM BE IDENTIFIED?

Most of the modifications to the trunk, limbs, hip, and the insertion of the vertebral column in the skull are related to bipedalism, which distinguishes our species from the apes.

Bipedalism can be detected in the fossil record by means of several anatomic evidences, as well as some footprints exceptionally conserved. However, its adaptive advantages are far from being clear. Charles Darwin suggested a hypothesis that related bipedalism, free hands, and tool use to the extent that their combination would amount

to a single complex phenomenon with morphological and functional aspects (Darwin, 1871). But, as Tobias (1965) noted, bipedalism is not a requisite for making or using tools. Chimpanzees use instruments quite ably, and they do so sitting up. The essential element in the relation between posture and the use of cultural elements is upright posture, not bipedalism. But there is more. Bipedalism appeared in human evolution long before culture.

Different hypotheses concerning the adaptive advantages of bipedalism in precultural conditions, without reference to tool use, have been proposed (see Tuttle et al., 1990). We have retained the original names used by Tuttle et al. (1990), referred to concepts expressed in a pretty casual tone. But that does not mean they should not be taken seriously. For instance, studies on the mechanics of locomotion have shown the benefits of the bipedal solution in terms of energetic economy (Kimura et al., 1979; Reynolds, 1985).

As Tuttle et al. (1990) noted, it is possible that several factors provided adaptive advantages and that some, or many, of them combined to achieve the result of bipedal behavior. There are two separate issues underlying the search for hypotheses to explain the adaptive advantage of bipedalism. The first issue concerns the circumstances behind the appearance of the first bipedal behaviors in a tropical forest environment. The second issue concerns the benefits of bipedalism as an adaptation to the savanna. These two questions must not be confounded: bipedal behavior existed long before savannas were extensive in the Rift Valley. The two questions are often confounded by seeking a "general explanation of bipedalism." The hypotheses summarized in Tuttle et al. (1990) classification refer to the adaptive advantages of bipedalism in the savanna, not on the forest floor. Thus, they are inadequate to explain the reason for an upright locomotion, unless this evolution is considered to have taken place only during the last 2.5 Ma.

Yves Coppens suggested the progressive reduction of the tropical forest thickness as a possible explanation for the gradual evolution of bipedalism. If the distance among the trees gradually increased, it would become necessary to travel longer distances on the ground to go from one to another. At the same time it would be imperative to retain the locomotor means for climbing. Distinct functional responses appeared in the different lineages leading to current primates: knuckle-walking bipedalism in the ancestors of gorillas and chimpanzees and an incipient bipedalism in the first hominins (Coppens, 1983b, 1991; Senut, 1991).

The gradual substitution of forests for open savanna spaces would be an increasing selective pressure toward more complete bipedalism, functionally speaking. The final result of this process was two evolutionary lineages of bipedal primates based on different adaptive strategies, close to 3.5 Ma. One million years later this divergence would increase with the decrease in temperatures and the appearance of extremely robust australopiths and the genus *Homo*.

The explanation given by Coppens and Senut has a considerable advantage: simplicity. Brigitte Senut noted that the locomotor hypothesis of the origin of bipedalism has been among the least favored. This hypothesis suggests that hominins had become bipedal for reasons strictly associated with locomotion itself (Senut, 1991), that is to say, the need for traveling on the ground of open forests. Senut explored eight hypothetical ways in which bipedalism could have originated from the locomotion of other primates, but ended up developing with greater detail the explanation favored by Coppens (1983a,b).

Senut (1991) has argued that the comparative examination of fossil specimens and current great apes does not lead to definitive conclusions. The combination of traits observed in fossil hominin species suggests that their locomotor habit would be very different from the very specialized locomotion of current great apes. If so, the only clues regarding the evolution of bipedalism are provided by fossil hip and limb postcranial remains of Miocene and early Pliocene members of our tribe, australopiths. The answers concerning the evolution of bipedalism depend on the analysis of these morphological traits in early and current specimens of our lineage. If they are similar but not identical, what do the differences mean phylogenetically?

"PARTIAL" VERSUS "COMPLETE" BIPEDALISM

Hominin bipedalism is thought to have developed in several stages from the incipient bipedalism of early australopiths to the complete bipedalism of the specimen found in Java by Dubois, *Homo erectus*. But this is not the only possible interpretation. There are authors who reject the idea that there were different stages in the evolution of bipedalism along the hominin lineage. For instance, the comparative examination of the tibia of australopith specimens from Olduvai (Tanzania), Koobi Fora (Kenya), and Hadar (Ethiopia) led—as we pointed out earlier—Owen Lovejoy, renowned specialist in hominin locomotor patterns, to the conclusion that the bipedal locomotion of early hominins was as developed as our own (Lovejoy, 1975; Latimer et al., 1987). The study of australopith specimens from South Africa also indicated, according to Lovejoy (1975), that there is no morphological reason to consider that their locomotion was "intermediate" between that of African apes and modern humans. The morphology of the pelvis of those early hominins is very similar to that of living current humans, according to this author. Their illium is equivalent to that of human beings (this, by the way, had already been noted since the discovery of the first

exemplars—Dart, 1949—and generally admitted since then). The differences observed in their ischium probably have no functional consequences. And the pubis, in any case, has little bearing on the question of locomotion.

The idea that the very wide pelvis of australopiths would have been favorable for bipedal locomotion has been rejected, however, by Christine Berge (1991) after the examination of the AL 288-1 specimen from Hadar (Ethiopia). At the level of the iliac crests and the pelvic cavity, the pelvis of AL 288-1 is much wider than that of modern humans. In Berge's biomechanical reconstruction, the long neck of the femur, acting as a lever arm, does not constitute an advantage, as Lovejoy surmised; rather, it introduces balancing problems. The vertical of the center of gravity would fall, in the case of *Australopithecus afarensis*, far from the knee articulation when leaning on one foot while traveling, leading to a greater instability of the lower limb (Berge, 1991). As a consequence, the kind of bipedal locomotion exhibited by *A. afarensis* would have required a higher degree of hip rotation to place the leaning knee within the body's vertical axis. In her morphometric study of the mobility of the hip of *A. afarensis*, and in order to obviate the difference in height between *Lucy* and current humans, Berge carried out the comparison with the pelvis of a pigmy woman 137 cm tall.

Regarding the possible reconstruction of the insertion of the gluteus in the hip of AL 288-1, Berge (1991) pointed out a noteworthy circumstance. Not much is known about that insertion, but the two possible alternatives are the "human" way, with the *gluteus maximus* inserted in the illium, and the "ape" way, in which the muscle would be inserted for the most part in the ischium. When Berge reconstructed the internal rotation movements of the thigh, she argued that the hip's morphology, together with the "human" reconstruction of the *gluteus maximus* insertion, would not allow AL 288-1 to perform the necessary movements for bipedalism. These could only be performed with an "ape" insertion of the gluteus. This point is especially important, given that the role of the *gluteus maximus* in the evolution of bipedalism had been considered in a different way by Sherwood Washburn (1967), who believed that the transition from quadrupedalism to bipedalism began precisely with "human" changes to the gluteus, and John Napier (1967), who believed that this change did not take place until later stages in the evolution of bipedalism and carried out functions related only with balance while running or going up slopes, but not walking. Berge's (1991) study supported Napier's point of view and concluded that the hip of AL 288-1 suggests that its locomotion included partially arboreal behavior.

Latimer et al. (1987) and Latimer (1991) have put forward an argument against the notion of australopith "partial" bipedalism, which, by the way, can be applied to any evolutionary process. They argue that the earliest hominins were bipedal, although they preserved some climbing traits. This claim is based on the fact that, within a Darwinian scenario, the persistence of primitive traits is not significant.

In Latimer's (1991) opinion, the functional value of primitive and derived traits is not the same. No arboreal primitive traits are retained by late Pliocene African great apes (Latimer and Lovejoy, 1989). This means, according to Latimer, that if australopiths are considered arboreal, they should be so based on certain derived traits that reveal the specific way in which they had adapted to their particular arboreal life. But all australopith-derived traits are related to bipedalism, not arboreality. Therefore, Latimer (1991) concluded that there can be no talk of "intermediate degrees" of bipedalism. Locomotion is determined by the new derived bipedal traits, while the presence of primitive characters must be understood as atavisms. Latimer (1991) believed this is supported by the morphology of the lower limbs, very evolved toward bipedalism, while primitive traits present in the upper limbs have little evolutionary significance.

THE TWO ADAPTIVE ADVANTAGES OF BIPEDALISM

Rejecting Lovejoy's notion of an advantage of australopith bipedalism has often led to the opposite conclusion. The bipedalism of early hominins is considered to be partial, something like a stage prior to development of complete bipedalism—which is believed to begin with *H. erectus,* such as the Trinil specimen. A partial bipedalism—like that described by Tuttle and Basmajian (1974)—is well adjusted to the morphology of australopith hands and feet and would be an adequate way to respond to the environmental demands of a tropical forest in which a considerable amount of traveling, but not all—and not even most of it—was done on the ground. But, is such locomotion a first step toward complete bipedalism?

Randall Susman and Jack Stern (1991) argue that the evolution of bipedalism was gradual and venture how it occurred differently in the gracile and robust australopith species. The earliest exemplars of our genus, *Homo habilis*, exhibit bipedal features in their feet (OH 8 from Olduvai, Tanzania), but their fingers (OH 7, OH 62) are functionally apt for climbing. However, Fred Spoor et al. (1994) have suggested a new way of studying the evolution of bipedalism: examination of the vestibular apparatus, the inner structure of the ear that is part of the system that controls movement. Using high resolution computerized tomography techniques, these authors analyzed the morphology of the bones of the semicircular canals of the ear in 31 current primate species, including our own and several higher apes, as well as different fossil specimens. Spoor et al. concluded that *H. erectus* was the

first species to exhibit an undoubtable modern human morphology. The dimensions of the australopith and paranthropine semicircular canal are similar to those of current higher apes. According to Spoor et al. (1994) *H. erectus* would necessarily be completely bipedal, while *Australopithecus africanus* had locomotor habits including optional bipedalism and arboreal climbing. Among australopiths, bipedalism would be a matter of posture and would not allow them to perform more complex movements, such as running or jumping.

The studies by Susman and Stern (1991), and Spoor et al. (1994), suggest that posture and balance differ between australopiths and the genus *Homo*. Patricia Kramer and Gerald Eck's (2000) study of the energetic balance of bipedalism puts the finger on the central question in the evolution of hominin locomotion. Can the same criterion be applied to calibrate the efficiency of different forms of hominin locomotion? From the point of view of our current locomotion, the way in which australopiths walked can seem inefficient. But the energetic balance of early bipedalism should be seen as an optimization to a different ecological niche. Thus, there would be two different adaptive strategies related with our lineage's bipedalism:

- "slow" bipedalism, characteristic of australopiths, with an excellent energetic balance in foraging tasks at low velocity, but inefficient for running at higher speeds;
- "fast" bipedalism, apt for running, with high energetic efficiency when great distances have to be traveled. This is the characteristic locomotion of *H. erectus* and later *Homo* taxa.

Accepting that the bipedalism of australopiths was different from that of modern humans does not imply that it was an incipient stage in human locomotion. This is theoretically robust, because intermediate stages do not make much evolutionary sense. Each taxon has evolved its own distinctive adaptations, which are, in this sense, final, rather than intermediate. A given species does not evolve a partial organ as an intermediate step toward later complete versions of it.

Within such a scheme, "slow" australopith bipedalism is not a transitory stage toward more developed locomotion processes. Morphological and functional indications suggest their locomotion was apt for individuals that lived in tropical forests and traveled short distances in their foraging activities. Sarmiento (1998) and Sarmiento and Marcus (2000) have proposed that Hadar australopiths would adopt quadrupedalism when they needed to move fast or travel long distances.

The importance of fast bipedalism in the evolution of the genus *Homo* has been brought to light in Dennis Bramble and Daniel Lieberman's (2004) study of the role of running. It is evident that current humans are not among the fastest animals in the savanna, nor were our hominin ancestors. However, running is related not only to speed itself. After comparing the metabolic costs of running and walking, Bramble and Lieberman (2004) conclude that several anatomical traits of the genus *Homo*—including narrow pelvis, long legs, short neck of the femur, and big toe—improved the energetic balance of fast bipedalism, running, because of enhanced features of fast marching: balance, thermoregulation, shock absorption, stress reduction, stabilization of the head and trunk, energy storage, and so on. The most important characteristic of running would be related with energy balance factors and not pure speed. This kind of locomotion would have been efficient for hunting and scavenging in open savannas when long distances had to be covered.

THE ORIGIN OF MODERN HUMANS

As we have seen, the study of fossil records, including using sophisticated models to evaluate the effectiveness of bipedalism, does not clarify the balance of chance and necessity in human evolution. Until a more complete picture is available of the evolution of genetic components along the phylogeny of our lineage, we must content ourselves with necessarily incomplete functional explanations of human distinctive traits and their adaptive scope. A direct comparison with our closest living siblings is the only resource that gives us firm evidence regarding functional explanations.

At the level of molecular expression it is already possible to identify some differences in the expressions of tissues. Logically, the picture is partial, because tissues are usually the result of the expression of different genes. Even so, differential gene expression patterns have been identified in the brains of humans and chimpanzees (Marqués-Bonet et al., 2004) and to a greater degree in their livers (Hsieh et al., 2003).

Paradoxically, the comparison of the members of our species with our closest relatives, gorillas and chimpanzees, produces, as we have seen, contradictory results: both are very similar to or very different from humans, depending on the chosen trait. Humans and chimpanzees are 99% identical in the overlapping genome regions, and 29% of the enzymes and other proteins encoded by the genes are identical in both species. The nonidentical proteins differ between humans and chimps by only two amino acids, on the average. Concluding that minor protein differences and 1% DNA sequence difference imply a virtual biological identity between chimpanzees and humans would, however, ignore the immense importance of development processes.

Epigenetic processes can modify the genetic background allowing to express, or not, the way in which environmental challenges are solved to allow any organism

to each adaptive fitness. How these epigenetic processes might have evolved into the human lineage is something very difficult to explain. However, the recovery of the ancient DNA of species of the human lineage closely related with the moment of appearance of modern humans, has opened a promising field of study.

Usually included in modern *H. sapiens* are modern humans and their ancestors that are not ancestors of *Homo neanderthalensis* as well. To be able to identify whether any other fossil specimen belongs in our species, we need to define the apomorphies of *H. sapiens*. It seems easy to identify the traits characteristic of modern humans, because we have an immense number of exemplars. But their abundance entails enormous intraspecific variation, which handicaps any effort to establish quantitative measurements. Consider, for example, the paradox faced by Stringer et al. (1984) seeking to specify the cranial measurements of *H. sapiens*. If bounds are used that would distinguish modern humans and their direct ancestors from other taxa, those bounds would exclude many living humans from the taxon. The issue is not, of course, how to know who is human and who is not. Fortunately the ethnocentrism of past generations that classified the "inferior races" as arboreal primates has long ago disappeared. The issue, however, is how to identify the taxon of "modern humans" so that we can decide whether particular fossils belong or not within the taxon, when this is not readily obvious.

In order to identify valid human apomorphies, we need to compare the traits of modern humans with those of our sister taxon, *H. neanderthalensis*—assuming, of course, that this taxon is a different species. William Howells (1973, 1989) made that comparison with respect to cranial measurements. More generally, Wood and Richmond (2000) have listed the apomorphies of *H. sapiens*. These apomorphies, as noted by Wood and Richmond, seem to fit best modern humans from hot, arid climates. This is hardly surprising since modern humans evolved in tropical Africa and their earlier expansion was through tropical or subtropical lands.

Molecular genetics has become, over the last few decades, a powerful method for investigating evolutionary questions. With respect to the origin of modern humans, it makes it possible to investigate three important issues: (1) time of origin: when did modern humans evolve? (2) place of origin: where did modern humans evolve? and (3) demography: how large was the original population of modern humans? Mitochondrial DNA (mtDNA) investigations placed the origin of modern humans in Africa, the time of origin between 150,000 and 200,000 years ago, and a mean population size that ranges between 10,000 and more than 50,000 individuals throughout the Pleistocene (see Cela-Conde and Ayala, 2007, Chapter 9).

TABLE 1.2 Nucleotide Substitutions and Deletions in the Comparison of Neandertal and Modern Human Genome With the Genome of the Chimpanzee (Green et al., 2010)

	Substitutions	Deletions
Modern human genome	10,535,445	479,863
Neandertal genome	3,202,190	69,029
Percentage	30%	14%

The development of techniques to recover ancient DNA has allowed us to obtain not only mitochondrial genetic material but also nuclear. The high resolution polymerase chain reaction (PCR) technique permitted the recovery from Neandertal specimen Vi-80 of Vindija (Croatia), a total of 254,953 sequences of nuclear DNA of around 1 million bp (0.03 of the total) (Green et al., 2006). This was the first important step in obtaining the Neandertal genome.

The complete recovery of the Neandertal genome was achieved by using PCR techniques on three Neandertal bone fragments—all of them females—from Vindija (Green et al., 2010). The comparison of the Neandertal genome with those from modern humans and chimpanzees has allowed inferring the number of nucleotide substitutions and deletions which occurred with respect to the chimpanzee genome shown in Table 1.2.

The great majority of substitutions and deletions found in the Neandertal genome (87.9% and 87.3%, respectively) occurred before its separation from the modern human lineage. Features derived in modern humans and primitive in Neandertals could be encoded by only 78 nucleotides whose substitution would have affected the structure of the protein, which, according to Green et al. (2010), indicates few changes at the level of amino acids during the several 100,000s of years that the two lineages, Neandertals and modern humans, have been separated. In order to understand the process of the hominin lineage evolution in its last segment, the comparison of single nucleotide polymorphisms (SNP)—polymorphisms in which the alleles differ in one or a few nucleotides—is the most relevant analysis.

Neandertals exhibit a similar range of SNP variation as modern humans in many regions of the genome; thus, both lineages share the same allele currently present in modern humans. However, in order to detect positive selection in modern humans, Green et al. (2010) focused on those SNPs that appeared as derived in our species, while Neandertals retained the plesiomorphy (shared with the chimpanzee genome)—ie, changes in the SNPs of the human lineage

TABLE 1.3 Genes Belonging to Regions With Single Nucleotide Polymorphisms Indicating a Likely Positive Selection in Modern Humans, With Defective Alleles Associated With Cognitive Disorders (Green et al., 2010)

Chromosome	Region	Genes	Associated Disorder
7	6,8662946–69,274,862	*AUTS2*	Autism
21	3,7580123–37,789,088	*DYRK1A*	Down syndrome
10	8,3336607–83,714,543	*NRG3*	Schizophrenia
6	4,5440283–45,705,503	*RUNX2*	Cleidocranial dysostosis
7	1,21763417–122,282,663	*CADPS2*	Autism

that emerged after its separation from the Neandertal lineage—by a process, therefore, of positive selection for the modern human lineage.

Green et al. (2010) identified a total of 212 regions which have likely experienced positive selection in *H. sapiens*. As there is a direct relationship between the strength of positive selection and the length of the affected sequence, the authors focused on 20 larger regions with positive selection SNPs, to identify the genes encoded by these nucleotide sequences. Five of the regions contained no protein-coding genes; the remaining 15 regions contained between 1 and 12 genes. The widest region, with an area of 336,000 bp, has very few derived SNPs in the Neandertal genome; this region is located on chromosome 2 and contains the *THADA* gene. Some alterations of this gene cause type II diabetes; Green et al. (2010) hypothesized a possible role of *THADA* in early modern humans which would affect energy metabolism regulation.

Table 1.3 shows different genes associated with conditions affecting cognitive capacity that belong to one of the 20 regions most likely to have undergone positive selection.

Obviously, positive selection is meaningless if it leads to select defective genes. The situation, however, is that in order to accommodate the need to direct medical research toward correlates between diseases and genes, the first gene function to be identified is altered. So far, functions performed by the genes of Table 20.4 in their nondefective version are unknown. However, it must be remembered that the Tim Crow evolutionary model on the origin of schizophrenia contemplates this disorder as a collateral and undesired outcome of gene positive selection, that, in their nondefective version, are related to language (see Crow, 1997, 2003, for example).

To verify the scope of Crow's hypothesis is beyond our current capabilities. It is unknown to what extent these genes are expressed in brain tissue, or even what meaning they might have with respect to cognitive functions. To pose the question whether the appearance of such human cognitive functions could be a random issue or due to adaptive advantages is speculative. However, using Illumina techniques to sequence ancient genomes has permitted the recovery of Neandertal nuclear DNA with an unexpected level of precision (Prufer et al., 2014). The starting material was a toe proximal phalanx of about 50,000 years age, found in Denisova Cave, Altai Mountains (Siberia, Russia) (Mednikova, 2011). Another very accurate retrieval of nuclear DNA, this time from a hand phalanx of an age of 48,000/30,000 years, found in Denisova Cave and attributed to an unknown group of archaic humans who have been called "Denisovans" (Meyer et al., 2012), provides us with genetic material of high quality from up to three species of humans from the late Paleolithic, enabling the comparison of some epigenetic processes in modern humans, Neandertals, and Denisovans.

As we have seen, one of the main epigenetic mechanisms of genetic alteration is DNA methylation, which consists in most cases in a change on the nucleobase cytosine preceding a guanine in the base sequence of the DNA chain (what is known as CpG dinucleotide). This change converts cytosine into thymine. The amount of CpG–TpG substitutions allows an estimate of the degree of methylation of a particular ancient genome (Gokhman et al., 2014).

David Gokhman et al. (2014) have reconstructed complete methylation maps of recovered Denisova DNA by comparing it with the current human genome. The authors identified ~2000 differentially methylated regions (DMRs), with substantial differences in the gene cluster *HOXD* due to methylation. This cluster is related to processes that lead to the development of the limbs. Gokhman et al. (2014) detected hypermethylation in the *HOXD9* promoter and in the *HOXD10* gene body of both, Neandertals and Denisovans. In turn, these regions are hypomethylated in all 37 bone samples of modern humans.

With regard to modern humans, the biggest difference in DMRs with respect to archaic humans—Denisovans and Neandertals—affects nervous, immune, cardiovascular, and

skeletal systems (Gokhman et al., 2014; supplementary materials). Moreover, Gokhman et al. (2014) indicated that "DMR-containing genes in present-day humans are almost twice as likely to be disease-related… More than a third of the disease-linked genes (30/81) are involved in neurological and psychiatric disorders." Once again, we are reminded of Crow's hypothesis, to which we referred earlier, relating the evolution of some specifically human cognitive capacities to their collateral consequences of having certain mental disorders.

At the current level of knowledge it is impossible to go beyond speculative explanations about the type of evolution, random or adaptive, which led to human cognitive differences. However, the DMRs identified by Gokhman et al. (2014) highlight the important role of epigenetics in fixing current human characteristics. The most important conclusion to be drawn is that the evolutionary models we use to explain the emergence of hominins and our own species may be too simple to portray the actual phylogenetic processes that occurred.

REFERENCES

Berge, C., 1991. Quelle est la signification fonctionelle du pelvis très large de *Australopithecus afarensis* (AL 288-1)? In: Coppens, Y., Senut, B. (Eds.), Origine(s) de la Bipédie Chez les Hominidés. Centre National de la Rechérche Scientifique, Paris, pp. 113–120.

Bramble, D.M., Lieberman, D.E., 2004. Endurance running and the evolution of *Homo*. Nature 432 (7015), 345–352.

Brunet, M., Guy, F., Pilbeam, D., et al., 2002. A new hominid from the Upper Miocene of Chad, Central Africa. Nature 418, 145–151.

Carroll, S.B., 2003. Genetics and the making of *Homo sapiens*. Nature 422, 849–857.

Cela-Conde, C., Ayala, F.J., 2007. Human Evolution. Trails From the Past. Oxford University Press, New York.

Cela-Conde, C.J., Gomila, A., Munar, E., et al., 2008. Taking Wittgenstein seriously. Indicators of the evolution of language. In: Smith, D.M.A., Smith, K., Ferrer-Cancho, R. (Eds.), The Evolution of Language: Proceedings of the 7th International Conference (EVOLANG7), Barcelona, pp. 407–408.

Chimpanzee Sequencing and Analysis Consortium, 2005. Initial sequence of the chimpanzee genome and comparison with the human genome. Nature 437 (7055), 69–87.

Choi, Y., Mango, S.E., 2014. Hunting for Darwin's gemmules and Lamarck's fluid: transgenerational signaling and histone methylation. Biochimica et Biophysica Acta (BBA) – Gene Regulatory Mechanisms 1839 (12), 1440–1453.

Coppens, Y., 1983a. Les plus anciens fossiles d'hominidés. Pontifical Academy of Science. Scripta Varia 50, 1–9.

Coppens, Y., 1983b. Systématique, phylogénie, environnement et culture des australopithèques, hypothèses et synthèse. Bulletin et Memoires de la Societé d'Anthropologie. Paris 10, 273–284.

Coppens, Y., 1991. L'évolution des hominidés, de leur locomotion et de leurs environnements. In: Coppens, Y., Senut, B. (Eds.), Origine(s) de la Bipédie Chez les Hominidés. Centre National de la Rechérche Scientifique, Paris, pp. 295–301.

Crow, T.J., 1997. Is schizophrenia the price that *Homo sapiens* pays for language? Schizophrenia Research 28, 127–141.

Crow, T.J., 2003. Genes for schizophrenia. The Lancet 361, 1829–1830.

Dart, R., 1949. Innominate fragments of *Australopithecus prometeus*. American Journal of Physical Anthropology 7, 301–334.

Darwin, C., 1871. The Descent of Man, and Selection in Relation to Sex. John Murray, London.

Dubois, E., 1894. Pithecanthropus erectus: Eine Menschanähnliche Übergangsform aus Java. Landsdruckerei, Batavia.

Dubois, E., 1935. On the gibbon-like appearance of *Pithecanthropus erectus*. In: Royal Acad., Proc, Amsterdam, p. 38.

Enard, W., Przeworski, M., Fisher, S.E., et al., 2002. Molecular evolution of *FOXP2*, a gene involved in speech and language. Nature 418, 869–872.

Gee, H., 1996. Box of bones 'clinches' identity of Piltdown paleontology hoaxer. Nature 381, 261–262.

Glazko, G., Veeramachaneni, G.G., Nei, M., et al., 2005. Eighty percent of proteins are different between humans and chimpanzees. Gene 346, 215–219.

Gokhman, D., Lavi, E., Prüfer, K., et al., 2014. Reconstructing the DNA methylation maps of the Neandertal and the Denisovan. Science 344 (6183), 523–527.

Goodman, M., Poulik, E., Poulik, M.D., 1960. Variations in the serum specifities of higher primates detected by two-dimensional starch-gel electrophoresis. Nature 188, 78–79.

Goodman, M., 1962. Evolution of the immunologic species specificity of human serum proteins. Human Biology 34, 104–150.

Goodman, M., 1963. Man's place in the phylogeny of the primates as reflected in serum proteins. In: Washburn, S.L. (Ed.), Classification and Human Evolution. Aldine, Chicago, pp. 204–234.

Green, R.E., Krause, J., Ptak, S.E., et al., 2006. Analysis of one million base pairs of Neanderthal DNA. Nature 444 (7117), 330–336.

Green, R.E., Krause, J., Briggs, A.W., et al., 2010. A draft sequence of the Neandertal genome. Science 328 (5979), 710–722.

Hattori, M., Fujiyama, A., Taylor, T.D., et al., 2000. The DNA sequence of human chromosome 21. Nature 405 (6784), 311–319.

Hedges, D.J., Callinan, P.A., Cordaux, R., et al., 2004. Differential *Alu* mobilization and polymorphism among the human and chimpanzee lineages. Genome Research 14, 1068–1075.

Howells, W.W., 1973. Cranial Variation in Man: A Study by Multivariate Analysis of Pattern of Differences Among Recent Human Populations. Harvard University Press, Cambridge, MA.

Howells, W.W., 1989. Skull Shapes and the Map: Craniometric Analysis of Modern Homo. Harvard University Press, Cambridge, MA.

Hsieh, W.P., Chu, T.M., Wolfinger, R.D., et al., 2003. Mixed-model reanalysis of primate data suggests tissue and species biases in oligonucleotide-based gene expression profiles. Genetics 165, 747–757.

International Human Genome Sequencing Consortium, 2001. Initial sequencing and analysis of the human genome. Nature 409 (6822), 860–921.

Khaitovich, P., Hellmann, I., Enard, W., et al., 2005. Parallel patterns of evolution in the genomes and transcriptomes of humans and chimpanzees. Science 309 (5742), 1850–1854.

Kimura, T., Okada, M., Ishida, H., 1979. Kinesiological characteristics of primate walking: its significance in human walking. In: Morbeck, M.R., Preuschoft, H., Gomberg, N. (Eds.), Environment, Behavior and Morphology: Dynamic Interactions in Primates. Gustav Fischer, New York, pp. 297–311.

Kramer, P.A., Eck, G.G., 2000. Locomotor energetics and leg length in hominid bipedality. Journal of Human Evolution 38, 651–666.

Latimer, B., Lovejoy, C.O., 1989. The calcaneus of *Australopithecus afarensis* and its implications in the evolution of bipedality. American Journal of Physical Anthropology 78, 369–386.

Latimer, B., Ohman, J.C., Lovejoy, C.O., 1987. Talocrural joint in African hominoids: implications for *Australopithecus afarensis*. American Journal of Physical Anthropology 74, 155–175.

Latimer, B., 1991. Locomotor adaptations in *Australopithecus afarensis*: the issue of arboreality. In: Coppens, Y., Senut, B. (Eds.), Origine(s) de la Bipédie Chez les Hominidés. Centre National de la Rechérche Scientifique, Paris, pp. 169–176.

Lovejoy, C.O., 1975. Biomechanical perspectives on the lower limb of early hominids. In: Tuttle, R.H. (Ed.), Primate Functional Morphology and Evolution. Mouton, The Hague, pp. 291–326.

Marqués-Bonet, T., Cáceres, M., Bertranpetit, J., et al., 2004. Chromosomal rearrangements and the genomic distribution of gene-expression divergence in humans and chimpanzees. Trends in Genetics 20, 524–529.

McBrearty, S., Jablonski, N.G., 2005. First fossil chimpanzee. Nature 437 (7055), 105–108.

Mednikova, M.B., 2011. A proximal pedal phalanx of a Paleolithic hominin from Denisova cave, Altai. Archaeology, Ethnology and Anthropology of Eurasia 39 (1), 129–138.

Meyer, M., Kircher, M., Gansauge, M.-T., et al., 2012. A high-coverage genome sequence from an archaic Denisovan individual. Science 338 (6104), 222–226.

Monod, J., 1970. Le hasard et la nécessité. Editions du Seuil, Paris. English Ed., 1971, Chance and Necessity. Knopf, New York.

Monod, J., 1971. Chance and Necessity. Knopf, New York, NY.

Napier, J., 1967. The antiquity of human walking. Scientific American 216, 56–66.

Navarro, A., Barton, N.H., 2003. Accumulating postzygotic isolation genes in parapatry: a new twist on chromosomal speciation. Evolution 57, 447–459.

Perry, G.H., Verrelli, B.C., Stone, A.C., 2005. Comparative analyses reveal a complex history of molecular evolution for human MYH16. Molecular Biology and Evolution 22, 379–382.

Pollard, K.S., Salama, S.R., Lambert, N., et al., 2006. An RNA gene expressed during cortical development evolved rapidly in humans. Nature 443, 167–172.

Prufer, K., Racimo, F., Patterson, N., et al., 2014. The complete genome sequence of a Neanderthal from the Altai Mountains. Nature 505 (7481), 43–49.

Pycraft, W.P., 1913. Ape-Man or Modern Man? Two Piltdown Skull Reconstructions. The Illustrated London News (September).

Reynolds, T.R., 1985. Mechanics of increased support of weight by the hindlimbs in primates. American Journal of Physical Anthropology 67, 335–349.

Rissman, E.F., Adli, M., 2014. Minireview: transgenerational epigenetic inheritance: focus on endocrine disrupting compounds. Endocrinology 155 (8), 2770–2780.

Ruvolo, M., 2004. Comparative primate genomics: the year of the chimpanzee. Current Opinion in Genetics & Development 14, 650–656.

Sarich, V., Wilson, A.C., 1967a. Immunological time scale for hominid evolution. Science 158, 1200–1203.

Sarich, V., Wilson, A.C., 1967b. Rates of albumin evolution in primates. Proceedings of the National Academy of Sciences 58, 142–148.

Sarmiento, E.E., Marcus, L.F., 2000. The os navicular of humans, great apes, OH 8, Hadar, and *Oreopithecus*: function, phylogeny, and multivariate analyses. American Museum Novitates 3288, 1–38.

Sarmiento, E.E., 1998. Generalized quadrupeds, committed bipeds, and the shift to open habitats: an evolutionary model of hominid divergence. American Museum Novitates 3250, 1–78.

Senut, B., Pickford, M., Gommery, D., et al., 2001. First hominid from the Miocene (Lukeino Formation, Kenya). Comptes Rendus de l'Académie des Sciences 332, 137–144.

Senut, B., 1991. Origine(s) de la bipédie humaine: approache paléontologique. In: Coppens, Y., Senut, B. (Eds.), Origine(s) de la Bipédie Chez les Hominidés. Centre National de la Rechérche Scientifique, Paris, pp. 245–258.

Sibley, C.G., Ahlquist, J.E., 1984. The phylogeny of the hominoid primates, as indicated by DNA-DNA hybridization. Journal of Molecular Evolution 20, 2–15.

Smith, K., 2006. Homing in on the genes for humanity. Nature 442 (7104), 725.

Spoor, F., Wood, B., Zonneveld, F., 1994. Implications of early hominid labyrinthine morphology for evolution of human bipedal locomotion. Nature 369, 645–648.

Stedman, H.H., Kozya, B.W., Nelson, A., et al., 2004. Myosin gene mutation correlates with anatomical changes in the human lineage. Nature 428, 415–418.

Stringer, C.B., Hublin, J.J., Vandermeersch, B., 1984. The origin of anatomically modern humans in Western Europe. In: Smith, F.H., Spencer, F. (Eds.), The Origins of Modern Humans: A World Survey of the Fossil Evidence. Alan R. Liss, New York, pp. 51–135.

Susman, R.L., Stern, J.T., 1991. Locomotor behavior of early hominids: epistemology and fossil evidence. In: Coppens, Y., Senut, B. (Eds.), Origine(s) de la Bipédie Chez les Hominidés. Centre National de la Rechérche Scientifique, Paris, pp. 121–131.

Tobias, P.V., 1965. *Australopithecus, Homo habilis*, tool-using and tool-making. South African Archaeological Bulletin 20, 167–192.

Tuttle, R.H., Basmajian, J.V., 1974. Electromyography of brachial muscles in *Pan gorilla* and hominid evolution. American Journal of Physical Anthropology 41, 71–90.

Tuttle, R.H., Webb, D., Tuttle, N.I., et al., 1990. Further progress on the Laetoli trails. Journal of Archaeological Science 17, 347–362.

Vallender, E.J., Lahn, B.T., 2004. Effects of chromosomal rearrangements on human-chimpanzee molecular evolution. Genomics 84, 757–761.

Washburn, S.L., 1967. Behaviour and the origin of man. Proceedings of the Royal Anthropological Institute of Great Britain and Ireland 1967, 21–27.

Watanabe, H., Fujiyama, A., Hattori, M., et al., 2004. DNA sequence and comparative analysis of chimpanzee chromosome 22. Nature 429 (6990), 382–388.

White, T.D., Asfaw, B., Beyene, Y., et al., 2009. *Ardipithecus ramidus* and the paleobiology of early hominids. Science 326 (5949), 29–40.

Wood, B., Richmond, B.G., 2000. Human evolution: taxonomy and paleobiology. Journal of Anatomy 196, 19–60.

Chapter 2

Hominins: Context, Origins, and Taxic Diversity

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HOMININS LOCATED IN THE TREE OF LIFE

The idea that the evolutionary history of the living world can be represented by a tree-like branching structure was one of Charles Darwin's many profound insights. All living taxa are on the tips of the branches that reach the surface of the Tree of Life (TOL) and all of the taxa that lived in the past are on branches within the TOL. Not that long ago it was assumed that the extant great apes—chimpanzees, bonobos, gorillas, and orangutans—were more closely related to each other than they were to modern humans. This was reflected in the premolecular taxonomy that placed modern humans in their own family, the Hominidae, and the great apes in a different family, the Pongidae. To reflect this family-level division, the informal term "hominid" was used to refer to modern humans and any extinct species considered to be more closely related to modern humans than to any of the great apes. The equivalent informal term for the great apes was "pongid."

Sequencing rapidly replaced hybridization as the method of choice for analyzing DNA and the number of sequence-based studies increases each year. There are now good draft sequences of the nuclear genomes of the chimpanzee (Consortium, 2005), orangutan (Locke et al., 2011), gorilla (Scally et al., 2012), and bonobo (Prüfer et al., 2012). Both DNA and morphological evidence (Shoshani et al., 1996; Gibbs et al., 2002; Lockwood et al., 2004; Diogo and Wood, 2011) can be used to generate hypotheses about the relationships among living hominoids, and both lines of evidence are consistent with the hypothesis that chimpanzees/bonobos are more closely related to modern humans than they are to gorillas. These new relationships are reflected in postmolecular taxonomies. The one we use in this review demotes modern humans from their own family to their own tribe, the Hominini. This means that the term "hominin" should now be used to refer to modern humans and any extinct species considered to be more closely related to modern humans than to any of the great apes.

If these molecular differences are calibrated using paleontological evidence for the split between the apes and the Old World Monkeys, and if we make the assumption that most of the DNA differences are neutral, this suggests that the hypothetical ancestor of modern humans and chimpanzees/bonobos lived between about 5 and 8 Ma and probably closer to 5 than to 8 Ma (Bradley, 2008). Estimates based on empirical data about generation times (Langergraber et al., 2012) and mutation rates (Venn et al., 2014) suggested that the date may closer to 8 and 13 Ma, respectively, but the most recent analysis of a larger data set (Prado-Martinez et al., 2013) lends support to the original estimate of c.5 Ma. Recalibration of the molecular clock to take account of the Oligocene catarrhine *Rukwapithecus fleaglei*, which has been argued to be a basal hominoid (Stevens et al., 2013), could further influence these estimates.

CANDIDATES FOR THE STEM HOMININ

Four different taxa have been proposed to be the stem hominin (ie, most recent common ancestor of all later hominins). We consider them in the order of their discovery rather than in their temporal order as judged from the date of their first appearance in the fossil record. For each species we will assess the claim that it (1) belongs to the hominin clade and that (2) it is the stem hominin.

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00002-8

Ardipithecus ramidus

The first putative hominin species we consider, *Ardipithecus ramidus*, was established to accommodate cranial and postcranial fossils recovered from c.4.5–4.4 Ma localities at Aramis on the northeastern flank of the Central Awash Complex in the Middle Awash study area, Ethiopia. The authors claimed *Ar. ramidus* shares some features with living species of *Pan*, others with the African apes in general, and, crucially, they suggest that several dental and cranial features are shared only with later hominins such as *Australopithecus afarensis*. The taxon was initially included within the genus *Australopithecus* (White et al., 1994), but it was subsequently transferred to a new genus, *Ardipithecus* (White et al., 1995). The first reported additions to the *Ar. ramidus* hypodigm came from the Gona study area (Semaw et al., 2005), but subsequently more fossils, including the ARA-VP-6/500 associated skeleton recovered from the Aramis locality (White et al., 2009), as well as fossils from two other localities, Kuseralee Dora and Sagantole, in the Central Awash Complex, have also been added to the hypodigm (White et al., 2009).

The chewing teeth of *Ar. ramidus* are relatively small and the form of the reconstructed pelvis and the morphology of the lateral side of the foot have been cited as evidence that the posture and gait of *Ar. ramidus* were, respectively, more upright and bipedal than is the case in the living apes. The enamel covering on the teeth is not as thin as that of chimpanzees/bonobos, but it is not as thick as that seen in archaic (*sensu* Wood, 2010) hominins such as *Au. afarensis* Suwa et al. (2009), and according to Rak et al. (2007) the morphology of the ramus of the mandible is similar to that of *Pan*. Initial estimates based on the size of the shoulder joint suggested that *Ar. ramidus* weighed c.40 kg, but its discoverers claim the enlarged hypodigm indicates an estimated mean body mass of c.50 kg (Lovejoy et al., 2009). Estimates by Grabowski et al. (2015) and Almécija et al. (2015) suggest a smaller (c.32 and c.36 kg, respectively) rather than a larger body mass.

With hindsight, the remains from Aramis may not be the first evidence of this species to be found, for the mandibular fragments from Lothagam (KNM-LT 329) and Tabarin (KNM-TH 13150) in Kenya, dated to c.5 Ma and 4.8–4.4 Ma, respectively, may prove to belong to *Ar. ramidus*.

Orrorin tugenensis

The next putative stem hominin is *Orrorin tugenensis* (Senut et al., 2001), the genus and species established to accommodate cranial and postcranial remains recovered from c.6.0 Ma Lukeino Formation sediments exposed at Aragai, Cheboit, Kapcheberek, and Kapsomin in the Baringo District, Kenya. The femoral morphology has been interpreted to mean that *O. tugenensis* was at least a facultative biped (Pickford et al., 2002; Richmond and Jungers, 2008; Almécija et al., 2013) but other researchers interpret the internal structure of the femoral neck as indicating a mix of bipedal and nonbipedal locomotion (Galik et al., 2004; Ohman et al., 2005). Almécija et al. (2010) suggested that the palmar surface of the pollical distal phalanx of *O. tugenensis* (BAR 1901′01) shows evidence of a flexor pollicis longus insertion that is modern human-like. Otherwise, the discoverers admit that much of the taxonomically critical dental morphology is "ape-like" (Senut et al., 2001, p. 6).

Sahelanthropus tchadensis

The third putative stem hominin is *Sahelanthropus tchadensis*. Six fossils, including the type specimen, an adult cranium (TM 266-01-060-1), and part of a mandible, were recovered in 2001 from a single locality, TM 266, in the Anthracotheriid Unit at Toros-Menalla in Chad (Brunet et al., 2002). The initial biochronology-based age estimate of between c.7–6 Ma was based on the good match between the fauna in the Anthrocotheriid Unit and the faunas known from Lukeino and from the Nawata Formation at the site of Lothagam in Kenya. More recently the results of cosmogenic nuclide dating that uses isotopes of beryllium ($^{10}Be/^{9}Be$) suggest that the Toros-Menalla locality is older than 6.83 ± 0.45 Ma and younger than 7.04 ± 0.18 Ma (Lebatard et al., 2008).

The cranium of *S. tchadensis* is chimp-sized and displays a novel combination of primitive and derived features. Much about the cranial base and neurocranium is chimp-like, with the exception that the foramen magnum lies more anteriorly than is generally the case in chimpanzees, but its position is in the overlap of the range for bonobos and modern humans (Ahern, 2005). The presence of a supraorbital torus, a relatively flat lateral profile of the face, small, apically worn, canines, low, rounded, molar cusps, relatively thick enamel, and a relatively thick mandibular corpus, were all cited by its discoverers as features that exclude *S. tchadensis* from any close relationship with the *Pan* clade.

More fossils assigned to *S. tchadensis* were recovered in 2001 and 2002. The additional specimens included an upper premolar tooth from TM 266, and mandibles, TM 247-01-02 and TM 292-02-01, from two new localities (Brunet et al., 2005). This additional evidence means that a minimum of six, and a maximum of nine, individuals are known from the Toros-Menalla region of Chad. The new data were consistent with the hypothesis that a single species was being sampled that showed a mix of derived (eg, small canine crown, vertical mandibular symphysis) and primitive (eg, mandibular premolar root form, an upper canine/lower premolar honing mechanism) morphology with

respect to the hominin clade. According to Emonet et al. (2014) the subocclusal morphology is ape-like.

Zollikofer et al. (2005) applied the techniques of virtual reconstruction (images based on CT scans manipulated using sophisticated computer software) to the TM 266 cranium and claimed that the reconstructed cranium strengthened the claim that *S. tchadensis* is an early hominin. But their results can also be interpreted as weakening the case for *S. tchadensis* being a hominin, for the logic of their third "test" (p. 755 and Fig. 3) is flawed. They show it is not easy to convert TM 226 into either a *Pan* or a *Gorilla* cranium, but although the researchers do not formally test this, their data suggest that it would be even *more* difficult to convert TM 266 into a modern human.

The only reference to differences between *O. tugenensis* and *S. tchadensis* in Brunet et al. (2002) is where the authors note that *S. tchadensis* is distinct from the former taxon because it has upper I^1s "with multiple tubercles on the lingual fossa" and because the latter's upper canines are "non chimp-like" and show "extensive apical wear" (p. 146).

Ardipithecus kadabba

The final putative stem hominin is *Ardipithecus kadabba*. Fossils recovered from four localities (Saitune Dora, Alayla, Asa Koma, and Digiba Dora) in the Western Margin region of the Middle Awash study area were initially assigned to *Ar. ramidus* as a separate subspecies, *Ardipithecus ramidus kadabba* (Haile-Selassie, 2001), but subsequently that initial hypodigm, plus some additional specimens, were elevated to species rank (Haile-Selassie et al., 2004, 2009). The initial hypodigm consisted of a partial mandible, four isolated teeth, fragments of a left upper limb, and a proximal foot phalanx. In 2004 six more dental specimens recovered from five c.5.8–5.2 Ma localities in the Middle Awash study area in Ethiopia were added to the hypodigm.

The main differences between *Ar. kadabba* and *Ar. ramidus* are that the apical crests of the upper canine crown of the former taxon are longer and the P_3 crown outline of *Ar. kadabba* is more asymmetrical than is the case in *Ar. ramidus*. Haile-Selassie et al. (2004) suggest there is a morphocline in upper canine morphology with *Ar. kadabba* exhibiting the most ape-like morphology (see Fig. 2.1D in Haile-Selassie et al., 2004). Haile-Selassie (2001) also suggests that there are differences in upper canine morphology between *Ar. kadabba* and *O. tugenensis* with the later having more "primitive" upper canine crowns that "lack the elevated crown shoulders" of "*Ardipithecus* and all other hominids" (p. 180). The formal diagnosis of *Ar. kadabba* (Haile-Selassie et al., 2004) refers to differences between the upper canines of *Ar. kadabba* and *O. tugenensis*, with the former having "a more circular upper canine outline" (p. 1504), whereas the latter has an upper canine crown that is "relatively more elongate mesiodistally" (p. 1505). It is also claimed that there are differences with respect to the morphology of the lingual face of the crown of the upper canine with that of *Ar. kadabba* being "relatively flat," whereas there is "stronger hollowing" on the only upper canine of *O. tugenensis* (Haile-Selassie et al., 2004, p. 1504). The proximal foot phalanx (AME-VP-1/71) of *Ar. kadabba* is said to combine an ape-like curvature with a proximal joint surface like that of *Au. afarensis* (Haile-Selassie, 2001).

ASSESSING THE CLAIMS FOR HOMININ STATUS

For a taxon to be a viable stem hominin, several aspects of its morphology need to be features that we can be certain are only seen in true hominins. There are an impressive number of differences between the morphology of chimpanzees/bonobos and modern humans, but the differences between the earliest hominins and the late Miocene ancestors of chimpanzees/bonobos are likely to have been much more subtle. So what paleoanthropologists have to do is to focus on the features that distinguish modern humans and chimpanzees/bonobos and then trace these back in time. Some of these features, such as those linked with bipedalism, can be traced back a long way. Others, such as the relatively diminutive jaws and chewing teeth of modern humans, were acquired more recently and thus cannot be used to tell the difference between early hominins and the ancestors of chimpanzees/bonobos. The presumption is that the stem panin would have a projecting face, relatively small chewing teeth, relatively and absolutely large, sexually dimorphic, honed canine teeth, and a locomotor system adapted for arboreal quadrupedalism. The presumption about the taxon at the base of the hominin clade, on the other hand, is that it would have been distinguished by cranial and other skeletal adaptations for a predominantly upright posture and skeletal and other adaptations for a locomotor strategy that includes substantial bouts of bipedalism. These features would be combined with a masticatory apparatus that combines relatively larger chewing teeth and more modest-sized canines. These inferences are "working hypotheses" that will need to be reviewed and tested as the appropriate evidence is uncovered (Fig 2.1).

There is also the problem that the presence of only one, or even a few, of the features that possibly distinguish early hominins from early panins or from the members of any closely related extinct clades may not be sufficient to identify a fossil as a hominin or a panin. This is because there is evidence that primates, like many other groups of mammals, are prone to convergent evolution. This results in homoplasy, which is morphology that is shared by two or more taxa, but which is not seen in their most recent

FIGURE 2.1 The relationships among modern humans and the great apes. The approximate dates of each hypothetical common ancestor are based on the references cited in the text. In version A the only options for a 5 Ma fossil species that shares more morphology with modern humans and chimpanzees/bonobos than with gorillas is to be an ancestor of modern humans or chimpanzees/bonobos. In version B the species could also belong to an extinct clade more closely related to modern humans, or to chimpanzees/bonobos, or to a closely related but completely separate clade.

common ancestor. The fact of convergent evolution means that it is not impossible, indeed it may even be probable, that some of what many have come to regard as key morphological adaptations at the base of the hominin lineage may have arisen more than once. If that is the case, then what characterizes hominins (and panins and the other great ape lineages) may not be particular items of morphology, single characters, but particular combinations of characters. There is also the problem that being an ancestor of modern humans or chimpanzees/bonobos is not the only option for the taxa described above. They could also belong to a clade closely related to modern humans or chimpanzees/bonobos that has no living representative. So labeling any taxon, especially one that has a poor fossil record and that only samples a few individuals, as one of the earliest members of the hominin clade is always going to be a risky enterprise.

Given this context and what we know of the size of the fossil records of *Ar. ramidus*, *O. tugenensis*, *S. tchadensis*, and *Ar. kadabba*, and how little of the skeleton and dentition three of those hypodigms represent, the case for any of the four species being the stem hominin is weak. In addition, what we know of the geological ages of *O. tugenensis* and *S. tchadensis* would suggest that they are on the old side for a stem hominin. The hypodigm of *Ar. ramidus* is larger, and it includes an associated skeleton, but apart from the regions such as the foot where much of the morphology is difficult to square with terrestrial bipedalism, if *Ar. ramidus* is the ancestor of *Australopithecus anamensis*, it is difficult to see how the substantial morphological differences between *Ar. ramidus* and *Au. anamensis* could have evolved in the short interval that separates the youngest fossil evidence for *Ar. ramidus* from the oldest evidence for *Au. anamensis*.

LADDER OR BUSH?

The only extinct species that *have* to be within the TOL are the ones situated on the branches leading to living species. In the case of the hominin twig of the TOL there is just one living species, modern humans, so the only species that need to be in the hominin clade are the species in the lineage connecting modern humans with the hypothetical common ancestor of modern humans and chimpanzees/bonobos. We may also have nonancestral close relatives, but they are not necessary for our existence. A consequence of this minimalist scenario is that throughout human evolutionary history there only needs to be one hominin species representing that single lineage, and all of the time-successive species in that lineage would be ancestors of modern humans. In this ladder-like model there would be no hominin taxic diversity (ie, no evidence of more than one contemporary species within the hominin clade) and the appropriate null hypothesis about any new species recognized in the hominin fossil record is that it is an ancestor of modern humans. At the other end of the complexity spectrum are models of human evolution that expect hominins to be as diverse and speciose as some groups of large mammals (eg, Alcelaphines, Tragelaphines, elephants). In these "bushy" scenarios close nonancestral relatives outnumber ancestors. As a consequence, the null hypothesis about a newly recognized species in the hominin fossil record is very different. In a "bushy" scenario it is assumed to be a nonancestral close relative of modern humans until proved otherwise.

An example of a ladder-like scenario is the single species hypothesis (Wolpoff, 1968, 1971). Wolpoff used the principle of competitive exclusion (ie, only one species at a time can occupy a specific ecological niche) to suggest that human culture is such a specialized ecological niche that "no more than one culture-bearing hominid could have arisen and been maintained" (Wolpoff, 1968, p. 477). Later, he argued that tool use could only have occurred if a hominin was bipedal (Wolpoff, 1971) and both Washburn (1950) and Mayr (1950) assumed that all hominins, and only hominins, were bipedal, with the latter author suggesting that "when the *Homo*-line acquired upright posture it entered a completely different adaptive zone" (Mayr, 1950, p. 111). However, as more hominin fossils were discovered during the late 1960s and early 1970s, especially in East Africa, most researchers interpreted the new evidence as strengthening the case for the presence of two forms of early hominin, referred to informally as "gracile" and "robust." Gracile hominin species were allocated to either *Homo*, *Telanthropus*, or *Australopithecus*, and the robust species were allocated to *Paranthropus* or *Zinjanthropus*. Wolpoff (1968) argued that the differences between the gracile and robust australopiths were the result of sexual dimorphism in a single species, and thus they merited no taxonomic distinction. He initially made these arguments on the basis of evidence of australopiths from Southern African sites, but later he expanded them to include the early East African discoveries (Wolpoff, 1971). However, this interpretation of the fossil evidence implies that in Southern Africa the males and females of the same taxon were found at separate, though geographically close, sites, estimated to be approximately half a million years apart in time.

For many the discovery and recognition of *Telanthropus* was an effective refutation of the single species hypothesis because it provided at a single site, Swartkrans, evidence of a *Homo erectus*—like hominin alongside *Paranthropus robustus* (Broom and Robinson, 1950). But Wolpoff did not recognize *Telanthropus* as a distinct taxon, nor was he convinced *Telanthropus* and *Paranthropus* were synchronic. In 1976 came the demonstration that an early African *Homo erectus* cranium (KNM-ER 3733) and a *Paranthropus boisei* cranium (KNM-ER 406) had

been found effectively in situ in Koobi Fora in strata dated to c.1.7 Ma. These two specimens are so different in morphology that there has been no rational dissent from the hypothesis that they should be included in separate genera, and for most, but evidently not all researchers (see Hunt, 2003), their discovery provided a convincing refutation of the single species hypothesis.

The falsification of the single species hypothesis as applied to Plio-Pleistocene hominins, along with the expansion of the hominin fossil record, the introduction of new dating methods, and the widespread adoption of phylogenetic methods, has led to the general acceptance that at several periods in its evolutionary history the hominin clade has consisted of more than one lineage (Wood and Baker, 2011). But debates about hominin diversity in early *Homo,* and prior to the origin of *Homo*, continue to be polarized. Those on the diversity side of the scales cite hominin fossil evidence consistent with multiple hominin species in three time periods, between c.3.5−3.3 Ma (Leakey et al., 2001; Spoor et al., 2010; Haile-Selassie et al., 2015), c.2.5 Ma (Asfaw et al., 1999; Guy et al., 2008), and c.2.0−1.8 Ma (Leakey et al., 2012; Spoor et al., 2015). These interpretations have been challenged (eg, White, 2003; Smith, 2005; Ackermann and Smith, 2007; White et al., 2009; Lordkipanidze et al., 2013) by researchers who suggest that those who support hominin taxic diversity in those time periods did not successfully demonstrate that the hypodigms of the proposed "new" taxa lie outside the range of variation of existing taxa.

EVIDENCE OF TAXIC DIVERSITY WITHIN THE HOMININ CLADE

"Diversity" refers to difference, and most studies of taxonomic diversity interpret difference to mean looking at the factors that influence the numbers and variety of species within a given space and time, or the numbers and variety of species sampled through deep time (Rosenzweig, 1995). But hominin taxic diversity, in the sense we discuss it here, does not refer to diachronic diversity (ie, differences *through* time and space). Instead, it focuses on whether there is evidence of synchronic taxonomic diversity (ie, differences *across* time and space) at predetermined temporal intervals between the origin of the hominin clade and the present. In the main section of this review we assess taxic diversity across the hominin clade as a whole regardless of whether the species in a time interval are sympatric or allopatric. This section is an abridged version of Wood and Boyle (2016).

We assigned the species, site collections, and individual specimens listed in Table 2.1 to one or more of the time intervals described below. We exclude hypotheses about some hominin species that have been proposed that we, and to judge by the lack of citations, others consider to be idiosyncratic. We assigned the nonidiosyncratic taxa to one or more time intervals according to each taxon's first appearance datum (FAD), which is the date of a taxon's first appearance in the fossil record, and its last appearance datum (LAD), which is the date of that taxon's last occurrence in the fossil record. The time intervals have to be long enough to capture several taxa, but not so long that they are uninformative about diachronic changes in taxic diversity. We are aware that decisions about the length and the registration of the time intervals can potentially bias the outcome of the analysis, but when we repeated the exercise with the longer intervals (see below) registered 0.5 Ma later, and with the shorter intervals registered at 0.25 and 0.75 Ma, the outcome was not materially different. So, given this, plus the various reasons why the observed FADs and LADs are always likely to underestimate the time span of the species we consider (see Discussion), we suggest that our results are as robust as the available data allow. The allocations of species to time intervals are based on conservative versions of the FADs and LADs (Table 2.1, columns 1 and 3) as determined from the published ages of the fossils.

The first time interval includes the fossil evidence between c.7 and 5 Ma. Although we are not convinced that these taxa belong in the hominin clade (see earlier in this section and Wood and Harrison, 2011), we consider the three species in that time interval that have been claimed to be early hominins. The next two time intervals each span 1 million years (ie, 5.0−4.0 Ma and 4.0−3.0 Ma), and the next four span half a million years (ie, 3.0−2.5 Ma, 2.5−2.0 Ma, 2.0−1.5 Ma, and 1.5−1.0 Ma) to reflect the larger numbers of hominin species proposed post-3 Ma. We then consider evidence for diversity within the hominin clade between 1.0 and 0.25 Ma, and finally in the interval between 0.25 Ma and the present. If a taxon spans more than one of these time intervals we review the fossil and other lines of evidence for it in the earliest time interval.

After we have considered the hominin species, site collections, or even individual fossils that have been recognized as, or suggested to be, discrete evolutionary units within a time interval, we informally review the evidence for diversity as pairwise comparisons. Our attempts to rank these in terms of the degree of confidence we have in any proposed species difference reflect our interpretation of the literature and own judgment about the strength of each case. We readily concede that others may well come to different decisions, but given the multiple variables involved (eg, what anatomical regions are sampled by the hypodigm, sample size, preservation, etc.) it was not immediately clear to us how such judgments, especially when made across more than 5 million years of hominin evolution, can be standardized. We are investigating ways to do this (Fig. 2.2).

TABLE 2.1 First Appearance Dates (FAD) and Last Appearance Dates (LAD) Used to Allocate Species and Specimens to Time Intervals

Taxon	Conservative FAD	With Dating Error FAD	Conservative LAD	With Dating Error LAD
Ardipithecus kadabba	6.3 Ma	6.7 Ma	5.2 Ma	5.11 Ma
Ardipithecus ramidus	4.51 Ma	4.6 Ma	4.3 Ma	4.262 Ma
Australopithecus afarensis	3.7 Ma	3.89 Ma	3.0 Ma	2.9 Ma
Australopithecus africanus	3.0 Ma	4.02 Ma	2.4 Ma	1.9 Ma
Australopithecus anamensis	4.2 Ma	4.37 Ma	3.9 Ma	3.82 Ma
Australopithecus bahrelghazali	3.58 Ma	3.85 Ma	3.58 Ma	3.31 Ma
Australopithecus deyiremeda	3.5 Ma	3.596 Ma	3.3 Ma	3.33 Ma
Australopithecus garhi	2.5 Ma	–	2.45 Ma	2.488 Ma
Australopithecus sediba	1.98 Ma	2.05 Ma	1.98 Ma	1.91 Ma
Burtele foot	3.4 Ma	3.47 Ma	3.4 Ma	3.2 Ma
Denisovans	48.65 ka	50.63 ka	29.2 ka	28.84 ka
Homo antecessor	1.0 Ma	1.2 Ma	0.936 Ma	–
Homo erectus	1.81 Ma	1.85 Ma	27 ka	–
Homo ergaster	1.7 Ma	2.27 Ma	1.4 Ma	0.87 Ma
Homo floresiensis[a]	74 ka	108 ka	17 ka	16 ka
Homo georgicus	1.85 Ma	–	1.77 Ma	–
Homo habilis sensu stricto	2.35 Ma	2.6 Ma	1.65 Ma	–
Homo heidelbergensis	700 ka	–	100 ka	–
Homo helmei	260 ka	–	80 ka	–
Homo neanderthalensis	130 ka	197 ka	40 ka	39.22 ka
Homo rhodesiensis	600 ka	–	300 ka	–
Homo rudolfensis	2.0 Ma	2.09 Ma	1.95 Ma	1.78 Ma
Homo sapiens	195 ka	200 ka	Present	–
Kenyanthropus platyops	3.54 Ma	3.65 Ma	3.35 Ma	–
Ledi-Geraru	2.80 Ma	2.85 Ma	2.75 Ma	2.65 Ma
Orrorin tugenensis	6.0 Ma	6.14 Ma	5.7 Ma	5.52 Ma
Paranthropus aethiopicus	2.66 Ma	2.73 Ma	2.3 Ma	2.23 Ma
Paranthropus boisei	2.3 Ma	2.5 Ma	1.3 Ma	1.15 Ma
Paranthropus robustus	2.0 Ma	2.27 Ma	1.0 Ma	0.87 Ma
Sahelanthropus tchadensis	7.2 Ma	7.43 Ma	6.8 Ma	6.38 Ma
Sima de los Huesos (SH)	780 ka	–	427 ka	415 ka

For each hominin species, site collection, or individual fossil referred to in this review, we provide the ages that correspond to the consensus (column one) and more conservative (column two) first appearance dates, and to the consensus (column three) and more conservative (column four) last appearance dates. For clarity, experimental errors for the ages are not included.
[a]*More recent dates suggest that* H. floresiensis *is closer to 100 ka.*

7.0–5.0 MA

Evidence of Diversity

White et al. (2009) suggest that the morphological differences between *Ar. ramidus* and both *O. tugenensis* and *S. tchadensis* do not justify either of the latter two species being assigned to their own genus, so they proposed they should be transferred to the genus with priority (ie, *Ardipithecus*) as *Ardipithecus tugenensis* (Senut et al., 2001; White et al., 2009) and *Ardipithecus tchadensis*

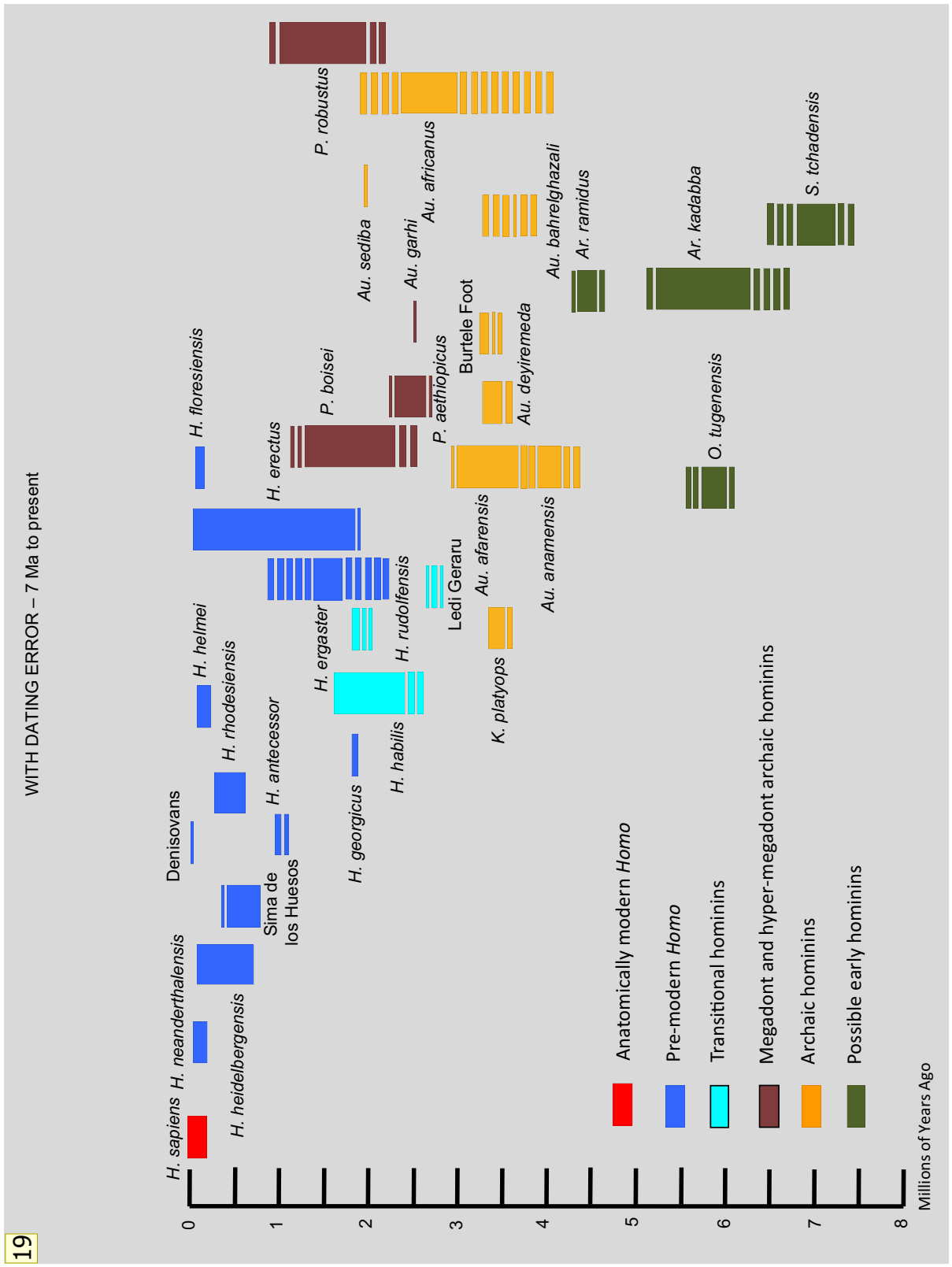

FIGURE 2.2 The hominin species, site collections, and individual fossils referred to in this review. The bottoms and tops of the continuous columns represent, respectively, the published first and last appearances dates. The tiles below and above many of the columns reflect the various sources of error that should be added to the mean ages that were used to locate the bottom and the top of each continuous column.

(Brunet et al., 2002; White et al., 2009), respectively. However, because White et al. (2009) did not question the decision to recognize *O. tugenensis* and *S. tchadensis* as separate species their proposal does not affect our consideration of taxic (ie, species level) diversity.

Since its initial description publications about *S. tchadensis* (eg, Zollikofer et al., 2005; Guy et al., 2005) have mainly focused on defending its status as a hominin rather than on defending the decision to recognize it as a species distinct from *O. tugenensis*. Zollikofer et al. (2005) and Guy et al. (2005) each emphasize the substantial (2500 km) distance separating the localities where the fossil evidence of the two taxa has been identified, but there is no a priori reason why the same taxon could not have existed in the two regions—see, for example, the later discussion about taxonomic diversity between *Au. afarensis* and *Australopithecus bahrelghazali*. When Brunet et al. (2005) described two new mandibles belonging to *S. tchadensis* they made no reference to how they compare with what is preserved of the mandibular morphology of *O. tugenensis*. However, apart from the mandible, and some positions along the maxillary tooth row, there is little overlap in the parts of the skeleton preserved in the two hypodigms.

In the paper establishing *Ar. kadabba* as a separate species (Haile-Selassie et al., 2004) the authors drew attention to differences between the crown morphology of the upper canines of *O. tugenensis* and *Ar. kadabba*, but in the summary they suggest that with respect to the dentition "*Sahelanthropus* and *Orrorin*… are very similar to *Ardipithecus kadabba*" (p. 1503). Also, when Haile-Selassie et al. (2009) reviewed the fossil evidence for *Ar. kadabba* they concluded that the mandibular morphology of *Sahelanthropus* is "broadly compatible with that exhibited by the ALA-VP-2/10 mandible (of *A. kadabba*)" (p. 208), but no evaluation of any similarities or differences between the mandibular morphology of *O. tugenensis* and *Ar. kadabba* was offered "because of the lack of detailed information" about *O. tugenensis* (p. 208). With respect to the postcanine dentition, Haile-Selassie et al. (2009) concluded that "the mandibular postcanine dentition of *Sahelanthropus* (TM266-02-154-2) closely matches the ALA-VP-2/10 equivalent in the available P_4 to M_3 metrics" (p. 218), and once again they offer no comparison with *O. tugenensis*. Yet, despite these acknowledged similarities, Haile-Selassie et al. (2009) do not advocate any change to the conventional taxonomy that recognizes species- and genus-level differences between *O. tugenensis*, *S. tchadensis*, and *Ar. kadabba*.

Given the small size of the hypodigms of the three proposed species, and the lack of overlap in the parts of the skeleton represented in those hypodigms, it would be unwise to assume that the fossils in this time interval sample three separate species. In our opinion the evidence for species differences (ie, taxic diversity) in this time interval is not as strong as is commonly assumed. The case for genus-level differences is even weaker.

5.0—4.0 MA

Australopithecus anamensis

Apart from the fossil evidence for *Ar. ramidus* reviewed in the previous section, the only other species from the 5.0—4.0 Ma time interval is *Au. anamensis* (Leakey et al., 1995). It was established to accommodate a left distal humeral fragment (KNM-KP 271) recovered in 1965 by Bryan Patterson at Kanapoi in Kenya (Patterson and Howells, 1967), plus cranial remains recovered in the 1990s from c.3.9—4.2 Ma localities at Allia Bay and Kanapoi. Additional fossils from Allia Bay and Kanapoi were described three years later (Leakey et al., 1998). Leakey et al. (1995) claimed that aspects of the dental morphology of the fossils collected at Allia Bay and Kanapoi are more primitive than those of *Au. afarensis* (eg, mandibular canine morphology, the asymmetry of the premolar crowns, and the relatively simple crowns of the deciduous first mandibular molars). White et al. (2006) attributed 31 fossils from the Middle Awash study area in Ethiopia to *Au. anamensis*. One, a maxilla, was found at Aramis, with the remainder coming from three localities at Asa Issie, a collecting area 10 km/6 miles west of Aramis, and biostratigraphic dating suggests an age of c.4.2—4.1 Ma for both sets of Middle Awash fossils. Craniodentally (eg, anterior tooth and postcanine relative tooth size, crown morphology, enamel thickness, etc.) the new material from the Middle Awash is consistent with an attribution to *Au. anamensis*. Upper limb remains have been recovered and were described as being australopith-like (Leakey et al., 1998), but a tibia (KNM-KP 29283) with features associated with obligate bipedalism that was attributed to *Au. anamensis* was not included in the list of paratypes. A specimen preserving the proximal three-quarters of a right femur shaft from Asa Issie (ASI-VP-5/154) looks like a slightly more primitive version of the *Au. afarensis* femoral morphology.

Evidence of Diversity

Evidence of taxic diversity within the 5.0—4.0 Ma time interval is dependent on being able to demonstrate significant differences between *Ar. ramidus* and *Au. anamensis*, yet even recent comparisons of *Ardipithecus* and *Australopithecus* (eg, White et al., 2009 and Suwa et al., 2009) are still between *Ar. ramidus* and *Au. afarensis*.

In their diagnosis of *Au. anamensis* Leakey et al. (1995) suggest that the new taxon "can be distinguished from *Ardipithecus*" because it has "absolutely and relatively

thicker tooth enamel; upper canine buccal enamel thickened apically; molars more buccolingually expanded; first and second lower molars not markedly different in size; tympanic tube extends only to the medial edge of the postglenoid process rather than to the lateral edge or beyond it; lateral trochlear ridge of humerus weak" (p. 565). These distinguishing features also occur in the list of inferred shared-derived characters that White et al. (2009) claim distinguish *Ar. ramidus* from *Au. anamensis* (Table 2.1: pp. 82–83).

Unlike the situation in the previous time interval there is substantial overlap in the parts of the skeleton represented by the hypodigms of *Ar. ramidus* and *Au. anamensis* with 7 out of 11 cranial and mandibular characters and 18 out of 34 dental characters that are in common in the two taxa differing, this strengthens the case for taxic diversity in this time interval.

4.0–3.0 MA

Australopithecus afarensis

The hominin species with historical priority in the 4.0–3.0 Ma time interval, *Au. afarensis* (Johanson et al., 1978; ICZN, 1999), was established to accommodate the c.3.7–3.0 Ma cranial and postcranial remains recovered from Laetoli, Tanzania, and Hadar, Ethiopia. When White et al. (1981) compared the hypodigms of *Au. afarensis* and *Australopithecus africanus* they made a compelling case for recognizing *Au. afarensis* as a distinct species whose craniodental anatomy is generally more primitive than that of *Au. africanus*. Kimbel et al. (1984, 2004) and Kimbel and Delezene (2009) provide further information about the morphological differences between *Au. afarensis* and *Au. africanus*.

To judge from the evidence of the associated skeleton AL 288-1, the hind limbs of *Au. afarensis* are substantially shorter than those of a modern human of similar stature, and the appearance of the pelvis and the relatively short lower limb suggest that while *Au. afarensis* was capable of bipedal walking it was poorly adapted for long-range bipedalism. The upper limb, especially the hand and the shoulder girdle, retains morphology that some workers suggest reflects a significant element of arboreal locomotion, yet Drapeau (2012) suggests that the *Au. afarensis* upper limb morphology was capable of the type of manipulation needed to manufacture crude artifacts. Recent body mass estimates for *Au. afarensis* range from c.30 to c.65 kg (Grabowski et al., 2015), endocranial volumes range between 385 and 550 cm^3, and estimates of the standing height of adult individuals range between 1.0 and 1.5 m. Reno et al. (2003) suggested that skeletal size sexual dimorphism in *Au. afarensis* is modest, but most researchers (eg, Gordon et al., 2008) accept that this taxon shows a substantial level of sexual dimorphism.

Australopithecus bahrelghazali

The second hominin species in this time interval, *Au. bahrelghazali* (Brunet et al., 1996), was established to accommodate a tooth-bearing midline mandible fragment plus an upper premolar tooth, both recovered from c.3.5–3.0 Ma sediments in the Bahr el Ghazal region, Koro Toro, Chad. The mandibular fragment was originally assigned to *Australopithecus* aff. *Australopithecus afarensis* (Brunet et al., 1995), but Brunet et al. (1996) assigned it to a new species because they claimed it had thicker enamel than *Ar. ramidus*, a more vertically oriented and more gracile symphysis than *Au. anamensis*, more complex premolar roots than *Au. afarensis*, and larger incisors and canines and more complex premolar roots than *Au. africanus*.

Kenyanthropus platyops

The next hominin species in the 4.0–3.0 Ma time interval, *Kenyanthropus platyops* (Leakey et al., 2001), was established to accommodate cranial remains recovered from the c.3.5 Ma Kataboi Member at Lomekwi, West Turkana, Kenya. The initial report lists the holotype cranium and the paratype maxilla. There also 34 other craniodental specimens, but the researchers reserved their judgment about the taxonomy of most of these remains (Leakey et al., 2001), some of which had only recently been referred to *Au. afarensis* (Brown et al., 2001). Leakey et al. (2001) did not assign the Lomekwi material to *Au. afarensis* because of its reduced subnasal prognathism, more anteriorly situated zygomatic root, the flatter and more vertically orientated malar region, the generally relatively small but thick-enameled molars, and the unusually small M^1 when compared to the size of the P^4 and M^3. The authors note the face of the new material resembles that of *Homo rudolfensis*, but they point out that the postcanine tooth row of the latter is substantially longer than that of KNM-WT 40000.

Australopithecus deyiremeda

The most recently proposed species in this time interval is *Australopithecus deyiremeda* (Haile-Selassie et al., 2015). It was established to accommodate several c.3.4 Ma cranial fossils including a left maxilla, part of the right maxilla from what might be the same individual, and two mandibles, all recovered from the Burtele (BRT) and Waytaleyta (WYT) collection areas in the Woranso-Mille study area in Ethiopia. The authors claim that the fossils assigned to *Au. deyiremeda* have thicker enamel, more complex P_4 roots, and a more robust mandibular corpus than *Ar. ramidus*, and when compared to *Au. anamensis* it has a mandibular symphysis that is more vertical, and a mandibular corpus that is more robust. Haile-Selassie et al. (2015) also claim

that the mandibular corpus of *Au. deyiremeda* lacks the lateral hollowing seen in *Au. afarensis*, the roots of the mandibular ramus and the zygomatic process of the maxilla are more anteriorly located, and the M^1 crown is smaller than is the case in *Au. afarensis*. They also suggest that the mandibular corpus of *Au. deyiremeda* is more robust and the root of the mandibular ramus is more anteriorly located than is the case in most of the mandibles attributed to early *Homo*. Dentally, *Au. deyiremeda* differs from *K. platyops* in having a larger canine, and from *Australopithecus garhi* because it has smaller canines and smaller postcanine tooth crowns.

Burtele Foot

The final evidence from this time interval is a partial foot (BRT-VP-2/73) recovered in 2009 from Burtele in the Woranso-Mille study area in Ethiopia (Haile-Selassie et al., 2012). What is notable about the foot is its opposable hallux, which, while obviously distinguishing it from the pedal remains of *Au. afarensis* (Haile-Selassie et al., 2010a,b, 2015; Ward et al., 2011) aligns it with the type of foot seen in *Ar. ramidus* (Lovejoy et al., 2009). Haile-Selassie et al. (2015) admit that they cannot reject the null hypothesis "that BRT-VP-2/73 belongs to *Au. deyiremeda*" (Supplementary Note 1), but the authors demur from assigning the foot to the new taxon because none of the fossil evidence for the latter "is clearly associated with BRT-VP-2/73" (p. 483).

Evidence of Diversity

In the past several decades researchers have assembled the substantial collection of fossils (now >400 specimens) that makes up the hypodigm of *Au. afarensis* (Kimbel and Delezene, 2009; Haile-Selassie et al., 2010a,b; Ward et al., 2012). Although there have been suggestions that the *Au. afarensis* hypodigm samples more than one taxon (Olson, 1981, 1985a,b; Senut, 1983; White et al., 1981; Tardieu, 1983), none of them have received support from the researchers most familiar with the evidence. Thus, any proposal for a new hominin species in the 4.0–3.0 Ma time interval must demonstrate that the morphology of the new fossil evidence lies outside of the envelope of morphological variation expected within the species represented by the various site samples of *Au. afarensis*.

When this test is applied to *Au. bahrelghazali*, while Guy et al. (2008) claim that the symphyseal outline of *Au. bahrelghazali* distinguishes it from *Au. afarensis*, others interpret the modest-sized hypodigm of *Au. bahrelghazali* as evidence of geographical variation within *Au. afarensis*. We agree with this assessment.

The proposal to establish a new species and genus, *K. platyops*, for fossil hominins discovered at West Turkana in 1998 and 1999 was based on the hypothesis that two specimens, the type, KNM-WT 40000, a 3.5 Ma cranium, and the paratype, KNM-WT 38350, a 3.3 Ma partial maxilla (Leakey et al., 2001) passed the test set out above. The case for rejecting *Au. afarensis* as the appropriate taxon for this material is made more complicated because the KNM-WT 40000 cranium is plastically deformed and permeated by matrix-filled cracks. White (2003) took the view that these factors are responsible for the unusual facial morphology, and he interprets KNM-WT 40000 as a taphonomically altered *Au. afarensis* cranium. Spoor et al. (2010) responded by making what, to us, is a convincing case that the matrix-filled cracking and deformation are not responsible for the observed differences. In any event the taphonomic alteration of the bone cannot explain the dental differences between KNM-WT 40000 and *Au. afarensis*.

The case made by Haile-Selassie et al. (2015) that *Au. deyiremeda* lies outside of the envelope of *Au. afarensis* has elements in common with the argument made by Leakey et al. (2001) for *K. platyops*. The authors claim that, compared with *Au. afarensis*, the mandibular corpus of *Au. deyiremeda* is more robust and lacks lateral hollowing and the roots of the mandibular ramus and the zygomatic process of the maxilla are more anteriorly located. With respect to the dentition they suggest that the postcanine tooth crowns are smaller and, as was the case for *K. platyops*, it is the M^1 crown that is particularly small. However, for many of the differences cited by Haile-Selassie et al. (2015) the condition in *Au. deyiremeda* is close to, or at the edge of the range of, the hypodigm of *Au. afarensis*. However, as good as that hypodigm is, it does not circumscribe the range of variation in that species. In our opinion the claim of distinctiveness would be much stronger if Haile-Selassie et al. (2015) had linked *Au. deyiremeda* with the foot from Burtele.

In their initial description of the Burtele foot, Haile-Selassie et al. (2012) noted that the short, opposable, hallux and overall morphology of the partial foot from Burtele are sound evidence that it "does not belong to the contemporaneous species *Au. afarensis*." They suggest that BRT-VP-2/73 retains "a grasping capacity that would allow it to exploit arboreal settings" (Haile-Selassie et al., 2012, p. 568), making it unlike the foot of *Au. afarensis* that has been described as "functionally like that of modern humans" and the foot of a "committed terrestrial biped" (Ward et al., 2011, p. 750). Thus, although the Burtele foot has not been formally assigned to a taxon, we suggest that the profound structural, and inferred functional, differences between BRT-VP-2/73 and the foot of *Au. afarensis* provide the strongest evidence for hominin taxic diversity in the 4.0–3.0 Ma time interval.

Several researchers have drawn attention to dental, facial, and mandibular differences between the early component of the *Au. afarensis* hypodigm from Laetoli and the geologically younger part of the hypodigm from Hadar,

and to similarities between the Laetoli remains and those of *Au. anamensis* (eg, Ward et al., 1999; Kimbel et al., 2006). It remains to be seen whether these similarities are sufficient evidence to sustain the hypothesis that *Au. anamensis* evolved via anagenesis into *Au. afarensis* (eg, Haile-Selassie et al., 2010a,b), but even if the taxa are related in this way it would have no effect on any claims about hominin taxic diversity because the fossil records of *Au. anamensis* and *Au. afarensis* are not synchronic.

3.0–2.5 MA

Australopithecus africanus

The first of the two species in the 3.0–2.5 Ma time interval, *Au. africanus* (Dart, 1925), was established to accommodate an immature skull recovered in 1924 from the limeworks at Taungs (now called Taung) in what is now South Africa. In addition to Taung the *Au. africanus* hypodigm as presently interpreted includes fossils from Member 4 at Sterkfontein, Members 3 and 4 at Makapansgat, and Gladysvale, all located in South Africa. It remains to be seen whether the associated skeleton StW 573 from Sterkfontein Member 2, and 12 hominin fossils recovered from the Jakovec Cavern (Partridge et al., 2003) belong to *Au. africanus*, or to a different species (Clarke, 2008). The cranium, mandible, and dentition of *Au. africanus* are well sampled and although the postcranial and the axial skeleton are less well represented there is at least one specimen of each long bone. However, many of the fossils have been crushed and deformed before they were fully hardened by fossilization.

Apart from the reduced canines the skull of *Au. africanus* is relatively ape-like. Its mean endocranial volume is c.460 cm^3. Morphological and functional analyses suggest that although *Au. africanus* was capable of walking bipedally it was probably more arboreal than most other archaic hominin taxa. The Sterkfontein evidence suggests that males and females of *Au. africanus* differed substantially in body size, but probably not to the degree they did in *Au. afarensis.*

Several researchers have commented on the unusual nature and degree of variation within the hypodigm of *Au. africanus* (Lockwood and Tobias, 2002), but there has been scant agreement on how the specimens that make up the hypodigm would be partitioned. Clarke (1988, 1999, 2008) has consistently argued that the Sterkfontein Member 4 and Makapansgat hypodigm of *Au. africanus* samples a second, more *Paranthropus*-like, taxon. He includes Sts 1 and 71, StW 183, 252, 384, 498, and 505, and MLD 2 within the second species, which he refers to as *Australopithecus prometheus* (Granger et al., 2015), thus reviving the species name Dart (1948) used for the hominin fossils from Makapansgat. The differences between the second taxon and *Au. africanus* mainly relate to craniofacial structure and dental size (Clarke, 2008).

Paranthropus aethiopicus

The second species in the 3.0–2.5 Ma time interval is *Paraustralopithecus aethiopicus* (Arambourg and Coppens, 1968), now *Paranthropus aethiopicus* (Chamberlain and Wood, 1987). The latter is the species name used by researchers who do not recognize *Paraustralopithecus* as a separate genus, but who do consider that >2.3 Ma hypermegadont hominins from the Omo-Turkana Basin belong to a species that is distinct from *Paranthropus boisei*. In addition to the type specimen the hypodigm includes a well-preserved adult cranium (KNM-WT 17000) and mandible (KNM-WT 16005) from West Turkana and isolated teeth from the Shungura Formation. Some also assign the juvenile braincase, L. 338y-6, from the Shungura Formation to this taxon. The only postcranial fossil considered part of the hypodigm of *P. aethiopicus* is a proximal tibia from Laetoli. Compared with *P. boisei* the face of *P. aethiopicus* is more prognathic, the cranial base is less flexed, the incisors, as inferred from their preserved alveoli, are large, and the postcanine teeth, especially the mandibular premolars, are less morphologically specialized than those of *P. boisei* (Suwa, 1988).

LD 350-1

The only other hominin from the 3.0–2.5 Ma time interval is represented by a single specimen, LD 350-1, the left side of a 2.8–2.75 Ma adult hominin mandible, found in the Lee Adoyta region of the Ledi-Geraru research area in the Afar Regional State in Ethiopia (Villmoare et al., 2015). Before deciding to allocate the mandible, which preserves the crowns and roots of the canine through to the M_3, to *Homo* sp. the researchers compared it with *Au. afarensis*. Their judgment was that although it was within the size range of *Au. afarensis* and shared with it features such as a sloping symphysis and a robust inferior transverse torus, they suggested that it differed from *Au. afarensis* by having a less robust corpus that lacked lateral hollowing, plus the height of the corpus was consistent along the tooth row. Dentally, the P_3 of LD 350-1 is more symmetrical, the M_1/M_2 hypoconid is reduced, the M_1 has a C7, and the P_3/molar wear pattern is reversed (Villmoare et al., 2015). Villmoare et al. (2015) also suggest that the isolated left and right P_3-M_2 crowns of a single individual (KNM-ER 5431) from the upper Tulu Bor Member (ie, between 3.0 and 2.7 Ma) at Koobi Fora in Kenya, and nonrobust teeth from Mbs B-C of the Shungura Formation in Ethiopia, may belong to the same taxon as LD 350-1.

Evidence of Diversity

There is an excellent case for distinguishing between *P. aethiopicus* and both *Au. afarensis* and the LD 350-1 mandible. Villmoare et al. (2015) understandably focus on whether LD 350-1 differs from the existing hypodigm of *Au.*

afarensis and although the mandible does not currently overlap temporally with that hypodigm, for reasons we set out below, we believe it was a sensible strategy. This case, and the one for distinguishing between LD 350-1 and the synchronic remains of *Au. africanus* from Southern Africa, while weaker than the case for distinguishing between *P. aethiopicus* and *Au. afarensis* and LD 350-1, respectively, are both a good deal stronger than the case for taxic diversity within the conventional hypodigm of *Au. africanus*.

2.5–2.0 MA

Paranthropus boisei

The hominin species with historical priority in the 2.5–2.0 Ma time interval is *Zinjanthropus boisei* (Leakey, 1959), now *P. boisei* (Robinson, 1960). It has a comprehensive craniodental fossil record that includes an especially complete and well-preserved skull from Konso in Ethiopia (Suwa et al., 1997), several well-preserved crania, and many mandibles and isolated teeth. *P. boisei* is the only hominin species we know of that combines a massive, wide, flat, face, massive premolars and molars, and small anterior teeth. The face of *P. boisei* is wider than that of *P. robustus*, yet their endocranial brain volumes are similar. The mandible of *P. boisei* has a large and wide body or corpus and the tooth crowns apparently grow at a fast rate. Apart from a partial upper limb from Olduvai Gorge and two very fragmentary possible *P. boisei* partial skeletons from Koobi Fora, no other postcranial evidence can be attributed to *P. boisei* with any reliability, but some of the postcranial fossils from Bed I at Olduvai Gorge traditionally linked with *Homo habilis sensu lato* (see below) may belong to *P. boisei* (Wood, 1974; Wood and Constantino, 2007). The range of the size difference in the *P. boisei* hypodigm suggests a substantial degree of body-size dimorphism. The fossil record of *P. boisei* extends across about one million years of time during which there is little evidence of any consistent trends in the size or shape of the cranium, mandible, and dentition (Wood and Constantino, 2007).

Homo habilis sensu lato

The next species in this time interval, *Homo habilis* (Leakey et al., 1964), was established to accommodate non-megadont fossil hominins (OH 4, 6, 7, 8, 13, 14, and 16) recovered between 1959 and 1963 from Beds I and II at Olduvai Gorge in Tanzania. The authors claimed that the cranial and dental morphology and estimated endocranial volume of that collection of specimens, plus inferences made about the dexterity and locomotion of the type of animal it sampled, were enough to both distinguish the new taxon from *Au. africanus* and justify its inclusion in *Homo*. Subsequent discoveries at Olduvai (eg, OH 24, 62, and 65) and from other sites (eg, Koobi Fora: KNM-ER 1470, 1802, 1805, 1813, 3735; Sterkfontein: Stw 53; Swartkrans: SK 847; Hadar: AL 666-1) have also been assigned to, or affiliated with, *H. habilis*. The hypodigm set out above has a relatively wide range of cranial and dental morphology (eg, endocranial volume ranges from c.500 to c.800 cm^3). All of the crania in this group are wider across the base of the cranium than across the vault. Facial and mandibular morphology varies (eg, KNM-ER 1470 has a flat and wide midface, whereas KNM-ER 1813 is broadest across the upper face). Postcanine teeth also differ in size and crown morphology, with some mandibular premolars and molars being narrow buccolingually (eg, OH 7), whereas other mandibular premolar teeth within the hypodigm (eg, KNM-ER 1802) are buccolingually broader, and have larger talonids and more complex root systems. Some researchers consider the cranial variation within the hypodigm set out above to be excessive in scale and unlike the pattern of intraspecific variation seen in the African ape clade, and they suggest that *H. habilis sensu lato* subsumes two taxa, *Homo habilis sensu stricto* and *H. rudolfensis*.

Paranthropus aethiopicus

The third species in this time interval, *P. aethiopicus*, has already been reviewed.

Australopithecus garhi

The final species to be considered in the 2.5–2.0 Ma time interval, *Au. garhi*, was established to accommodate a fragmented cranium recovered from the c.2.5 Ma Hatayae Member of the Bouri Formation at the Bouri, Gamedah, and Matabaietu collection areas in the Middle Awash study area of Ethiopia (Asfaw et al., 1999). It combines a primitive cranium with large postcanine teeth, and especially large P^3s. However, unlike other hyper-megadont species such as *P. aethiopicus* and *P. boisei*, the incisors and canines of *Au. garhi* are also large and the enamel apparently lacks the extreme thickness seen in those taxa. A partial skeleton combining a long femur with a long forearm was found nearby, but it is not associated with the type of cranium (Asfaw et al., 1999) and these fossils have not been formally assigned to *Au. garhi*.

Evidence of Diversity

The effective synchronicity of *P. boisei* and *H. habilis sensu lato* (Leakey and Walker, 1976; Wood, 1991) is perhaps the single strongest evidence of taxic diversity in the hominin fossil record. Even researchers who fiercely criticize, and even deride, the notion of hominin taxic diversity (eg, White, 2003) are willing to accept this example.

There is only one fragmented cranium for *Au. garhi*, but the skeletal and dental differences between it and the cranial hypodigm of *P. boisei* suggest that the claim for a distinction between that taxon and *P. boisei* is also a strong one.

However, for various reasons, including sample size, the other claims for hominin taxic diversity in the 2.5–2.0 Ma time interval are less compelling. That does not mean there is no case, just that it is modest in comparison with the number and scale of the craniodental differences between *P. boisei* and *H. habilis sensu lato* that are inconsistent with the sort of intraspecific variation one would predict based on a comparative analysis of the African ape clade (Wood et al., 1991). The case for distinguishing between *P. aethiopicus* and *P. boisei* is much weaker than the case for distinguishing the latter from *H. habilis sensu lato*, but given that the fossil records of *P. aethiopicus* and *P. boisei* presently do not overlap in geological time, any decision to recognize these two taxa as separate species has no impact on the issue of hominin taxic diversity.

2.0–1.5 MA

Homo erectus

The first species to be considered in the 2.0–1.5 Ma time interval is *H. erectus*. In his initial publication of the Trinil remains, Dubois (1893) referred the skullcap to *Anthropopithecus erectus*, a choice of genus that reflected his initial conviction that he had discovered the remains of a fossil ape. But a year later he changed his mind and transferred the new species to a novel genus, *Pithecanthropus*. The discovery of the Trinil calotte was significant because of its small cranial capacity (c.940 cm^3), low brain case, and sharply angulated occipital region. Most of the discoveries made by Ralph von Koenigswald at Sangiran, also in Indonesia, were added to the hypodigm of *Pithecanthropus erectus* and fossils that had been recovered from what was then called Choukoutien (now called Zhoukoudian) and initially assigned to *Sinanthropus pekinensis* (Black, 1927) were compared with the *P. erectus* hypodigm. The researchers responsible for analyzing the two collections suggested that the Indonesian and Chinese hypodigms were "related to each other… in the same way as two different races of present mankind" (von Koenigswald and Weidenreich, 1939, p. 928) and a year later the latter author proposed the two hypodigms should be formally merged within a single genus and species, as *Homo erectus pekinensis* and *Homo erectus javanensis*, respectively (Weidenreich, 1940). Subsequently *Meganthropus palaeojavanicus* (Mayr, 1944, p. 14; Le Gros Clark, 1955, p. 86–87), *Atlanthropus* (Le Gros Clark, 1964, p. 112), and *Telanthropus* (Robinson, 1961) were transferred to *H. erectus*. Some researchers (eg, Kaifu et al., 2008) interpret *H. erectus* as a chronospecies that evolves through time, whereas others (eg, Widianto and Zeitoun, 2003) argue there are potential species-level differences between the Sangiran/Trinil hypodigms and the more recent evidence from Sambungmacan and Ngandong.

Paranthropus robustus

The second species in this time interval, *Paranthropus robustus* (Broom, 1938), was established to accommodate fossil hominins recovered in 1938 from what was then referred to as the "Phase II Breccia" (now called Member 3) at Kromdraai B, in Gauteng Province, South Africa. Most of the current hypodigm comes from Swartkrans (Mbs 1, 2, and 3) with other fossil evidence coming from South African caves called Cooper's, Drimolen, and Gondolin. Although the dentition is well represented in the hypodigm of *P. robustus*, most of the mandibles are crushed or distorted. The brain, face, and chewing teeth of *P. robustus* are larger than those of *Au. africanus*, yet the incisors and canines are smaller, and whereas *P. robustus* includes crania with ectocranial crests, there are no *Au. africanus* crania with unambiguous crests. What little is known about the postcranial skeleton of *P. robustus* suggests that the morphology of the pelvis and the hip joint are much like that of *Au. africanus*.

Paranthropus boisei and *Homo habilis sensu lato*

Both species were introduced in the previous time interval.

Homo ergaster

The next species in the 2.0–1.5 Ma time interval, *Homo ergaster* (Groves and Mazák, 1975), was established to accommodate fossil hominins recovered from Koobi Fora that, in the judgment of the authors, did not belong in the taxa known at the time. Wood (1994) used the taxon name *H. ergaster* for hominin remains (eg, KNM-ER 730, 820, and 992) that are generally more primitive and lack the more extreme expressions of some of the derived features (eg, thick inner and outer table, sagittal keeling, etc.) seen in Asian *H. erectus*.

Homo rudolfensis

If the fossils assigned to *H. habilis sensu lato* (see above) sample not one, but two species, and if that second species includes KNM-ER 1470, then the next species with historical priority in this time interval is *Pithecanthropus rudolfensis*, subsequently transferred to *Homo* (Groves, 1989) as *H. rudolfensis*. Leakey et al. (2012) described a face (KNM-ER 62000) and two mandibles (KNM-ER 1482 and 60000) that match KNM-ER 1470, and Spoor et al. (2015) make the case that the dental arcade of the enlarged

hypodigm of *H. rudolfensis* is distinctively different (eg, more divergent tooth rows, flatter anterior dental arch) from the dental arcade of *H. habilis sensu stricto*.

Homo georgicus

The penultimate species in this time interval, *Homo georgicus* (Gabounia et al., 2002), was established for the hominin fossils recovered from Dmanisi. The holotype is the mandible D2600. No paratypes were formally designated, but the mandible D211, the calvaria D2280, the cranium D2282, and the skull and associated skeleton D2700 were referred to as evidence that "will complete the characteristics of the new species" (Gabounia et al., 2002, p. 244). Although several of the authors of the original publication (eg, Lordkipanidze et al., 2013) no longer support a separate taxon for this material, we treat it separately in our discussion of the evidence in this time interval because the circumstances of the site are that the hominin evidence from Dmanisi provides a sense of the range of variation within what some think is a relatively short interval of time. Overall, the fossils are most similar to *H. erectus*, and where there are differences they involve morphology inferred to be more primitive than that seen in that taxon.

Australopithecus sediba

The final species in the 2.0—1.5 Ma time interval, *Australopithecus sediba* (Berger et al., 2010), was established to accommodate two associated skeletons, MH1, a sub-adult presumed male, and MH2, an adult presumed female, recovered from Malapa, Gauteng Province, in South Africa. Berger et al. (2010) suggested that *Au. sediba* has cranial (eg, more globular neurocranium, gracile face), mandibular (eg, more vertical symphyseal profile, a weak *mentum osseum*), dental (eg, simple canine crown, small anterior and postcanine tooth crowns), and pelvic (eg, acetabulocristal buttress, expanded ilium, and short ischium) morphology that departs from that seen in *Au. africanus*, and which is only shared with early and later *Homo* taxa. Carlson et al. (2011), Kivell et al. (2011), and Zipfel et al. (2011), make similar claims for *Au. sediba*'s endocranial, hand, and foot morphology, respectively.

Evidence of Diversity

There is little doubt that the fossil evidence assigned to *H. erectus*, *P. robustus*, and *Au. sediba* samples three different species. There is also compelling evidence to suggest that *P. boisei* is distinct from *P. robustus* (Tobias, 1967; Rak, 1983) and *H. habilis sensu lato* from *H. erectus* (*contra* Lordkipanidze et al., 2013), but the evidence for these latter distinctions, as convincing as it is, is not as clear-cut as the case for recognizing *H. erectus*, *P. robustus*, and *Au. sediba* as separate species.

The case for making specific distinctions among *H. erectus*, *H. ergaster*, and *H. georgicus* is weaker still. Two categories of features are claimed to distinguish *H. ergaster* from *H. erectus*. The first comprises dental features for which *H. ergaster* is more primitive than *H. erectus*, the second includes features of the cranial vault and cranial base that are less derived in *H. ergaster* than in *H. erectus*. For example, it is claimed that *H. ergaster* lacks some of the more derived features of *H. erectus* (eg, thickened inner and outer tables and prominent sagittal and angular tori (Wood, 1984, 1991)), but other researchers dispute the distinctiveness of this material, and Spoor et al. (2007) claim that the expression of some features is related to the overall size of the cranium such that larger *H. erectus* crania are more likely to show the derived morphology.

1.5—1.0 MA

Homo erectus, Paranthropus robustus, Paranthropus boisei, Homo habilis, and *Homo ergaster*

All of these species were reviewed in earlier time intervals.

Homo antecessor

The sixth species in this time interval, *Homo antecessor* (Bermúdez de Castro et al., 1997), was established to accommodate hominins recovered from level 6 of the Gran (or Trinchera) Dolina, a complex of caves in the Atapuerca hills near Burgos, Spain. The modern human-like morphology of the face and the apparent lack of derived *Homo neanderthalensis* features, combined with differences between the Gran Dolina hominins and *H. erectus*, led Bermúdez de Castro et al. (1997) to propose that the former fossils should be assigned to a new species, *H. antecessor*, which they suggest is probably the most recent common ancestor of *H. neanderthalensis* and *H. sapiens*. *H. antecessor* is included in this time interval because a c.1.2—1.1 Ma partial mandible (ATE9-1) from the Sima del Elefante was provisionally assigned to this species (Carbonell et al., 2008), and because a reappraisal of the Ceprano cranium has suggested that it may also belong to *H. antecessor* (Manzi et al., 2001). But *H. antecessor* is also included in the 1.0—0.25 Ma time interval because Bermudez de Castro et al. (2011) concluded there was not enough evidence to assign the Sima del Elefante mandible to *H. antecessor*.

Evidence of Diversity

The evidence for *H. erectus* and *P. boisei*, *H. erectus* and *P. robustus*, and *H. habilis sensu lato* and *P. boisei* being distinct species pairs is exceptionally strong. The case for distinguishing *P. boisei* and *P. robustus* is strong, but the scale of the morphological differences between them is much less than the differences between the three species comparisons listed above.

Despite the claims of Lordkipanidze et al. (2013), the case for distinguishing between *H. erectus* and *H. habilis sensu lato* is a strong one that involves detailed, and not so detailed, cranial, mandibular, dental, and postcranial differences. It is a substantially stronger case than the ones for distinguishing between *H. erectus* and *H. ergaster*, and between *H. antecessor* and *H. erectus*/*H. ergaster*.

1.0–0.25 MA

Homo erectus

The species with historical priority, *H. erectus*, was reviewed in an earlier time interval.

Homo heidelbergensis

The next species in this time interval, *Homo heidelbergensis* (Schoetensack, 1908), was created to accommodate a hominin mandible found in 1907 in a sandpit at Mauer, near Heidelberg in Germany. Schoetensack concluded that the Mauer mandible's mix of primitive (no chin, robust corpus, broad ramus, and an anterior–posteriorly deep mandibular symphysis) and derived (reduced canines and modern human-like dental proportions) features was sufficient to distinguish it from *Homo sapiens*, *H. neanderthalensis*, and what was then called *P. erectus*. But *H. heidelbergensis* attracted little interest until it was suggested that it might be the most appropriate species name for a group of Afro-European hominin fossils (eg, Arago, Bodo, Kabwe, Mauer, Ndutu, and Petralona) that had traditionally been labeled as "archaic" *H. sapiens* (Rightmire, 1995). Mounier et al. (2009) set out the morphological grounds for recognizing *H. heidelbergensis* as a taxon separate from *H. neanderthalensis*, *H. sapiens*, and *H. erectus*, as well as providing a definition and a differential diagnosis (p. 243–244). The "Afro-European" hypothesis interprets *H. heidelbergensis* as a geographically widely dispersed species that gave rise to *H. neanderthalensis* in Eurasia and *H. sapiens* in Africa, whereas the "European" hypothesis sees *H. heidelbergensis* restricted to Europe where it is only ancestral to *H. neanderthalensis* (Mounier et al., 2009). Other researchers (eg, Dean et al., 1998; Carbonell et al., 2005; Hublin, 2009) interpret *H. heidelbergensis* as representing an early stage in the accretion model for the origin of *H. neanderthalensis* (ie, it should be included in *H. neanderthalensis* if that taxon is interpreted inclusively) as a chronospecies.

Homo rhodesiensis

The third species in the 1.0–0.25 Ma time interval, *Homo rhodesiensis* (Woodward, 1921), was introduced to accommodate the cranium and limb bones (Kabwe 1 or E 686) recovered from the Broken Hill lead mine at Kabwe, in what then was the British protectorate of Northern Rhodesia, now Zambia. Woodward reasoned a new species was needed because Kabwe 1 was not as primitive as what we now refer to as *H. erectus*, nor as derived as either *H. sapiens* or *H. neanderthalensis*. Morphologically similar remains include fossils from Hopefield/Elandsfontein in southern Africa, Ndutu in Tanzania, Sale in North Africa, and Bodo in Ethiopia. The taxon *H. rhodesiensis* is used by researchers who see *H. heidelbergensis* as an exclusively European premodern *Homo* taxon (ie, the "European" hypothesis).

Homo helmei

The last formal species in the 1.0–0.25 Ma time interval, *Homo helmei* (Dreyer, 1935), was established for the Florisbad 1 partial cranium discovered in 1932 in Florisbad in South Africa. Some researchers interpret the cranium as being intermediate in morphology between *H. heidelbergensis* and *H. sapiens*, with its more steeply inclined frontal bone distinguishing it from the former, and its large brow ridge, more receding frontal, and low greatest breadth in the vault distinguishing it from anatomically modern humans. Others have suggested that Jebel Irhoud, Ngaloba (aka LH 18), and Omo II belong to the same hypodigm.

Sima de los Huesos

The penultimate group in this time interval is the unusually complete and well-preserved collection of hominins recovered from the Sima de los Huesos, one of the many breccia-filled cave systems that make up the Cueva Mayor-Cueva del Silo within the Sierra de Atapuerca, near Burgos in northern Spain. To date, more than 6500 hominin specimens belonging to at least 28 individuals (Bermúdez de Castro et al., 2004) have been recovered from excavations in the main cave and in the ramp that leads down to the cave. The hominin remains include numerous crania, mandibles, hundreds of teeth, a nearly complete pelvis, vertebrae, ribs, hand and foot bones, and multiple specimens of long bones. The cranial and mandibular sample shows a number of derived features of *H. neanderthalensis* (eg, pronounced mid-facial prognathism, the form of the brow ridge, a flat articular

eminence of the glenoid fossa, a retromolar space, and an asymmetrical configuration of the ramus of the mandible). In contrast, the cranial vault is generally more plesiomorphic (eg, large, projecting, mastoid processes, rounded neurocranium), with some incipient derived traits of *H. neanderthalensis* (eg, weak expression of the suprainiac fossa). The dentition is generally typical of *H. neanderthalensis* (Gómez-Robles et al., 2015).

Homo antecessor

This species was reviewed in the previous time interval.

Evidence of Diversity

The best evidence for taxic diversity in the 1.0—0.5 Ma time interval is the coexistence in time, if not in space, of *H. erectus* in China and Southeast Asia and *H. heidelbergensis* in Europe. As for hominin taxonomic diversity within Europe, researchers most familiar with the evidence from the Sima de los Huesos make a distinction between that site sample and the hypodigm of *H. neanderthalensis*, but even though they assigned the Sima de los Huesos hominins to *H. heidelbergensis* (Arsuaga et al., 1997) they acknowledged that *H. heidelbergensis* is related to the Neandertals in the same way that *Au. anamensis* is related to *Au. afarensis* (see earlier). Those who treat the fossils from the Sima de los Huesos as evidence of an early stage of an *H. neanderthalensis* chronospecies include them within that taxon (Hublin, 2009). As for *H. heidelbergensis* and *H. rhodesiensis*, the jury is still out on whether the latter is a junior synonym of the former, or a distinct taxon that was the common ancestor of both *H. neanderthalensis* and modern humans (see Fig. 2.1 in Hublin, 2009).

While some researchers suggest that Florisbad 1 could serve as the holotype of *H. helmei*, most take the view there is no satisfactory diagnosis for such a taxon that separates it from *H. heidelbergensis* (or from *H. rhodesiensis* if the distinction between *H. heidelbergensis* and *H. rhodesiensis* is accepted) or *H. sapiens*.

Finally, the case for distinguishing between *H. erectus*/*H. ergaster* and *H. antecessor* is inevitably weak because of the small hypodigm of the latter taxon.

0.25 MA TO THE PRESENT

Homo sapiens

The species with historical priority in this time interval is *H. sapiens* (Linnaeus, 1758). The first widely accepted fossil evidence of modern humans came in 1868 when a series of skeletal remains was discovered at the Cro-Magnon rock-shelter at Les Eyzies de Tayac in France. Since then, discoveries of *H. sapiens*—like fossils had been made elsewhere in Europe (eg, Mladec, Predmosti, and Brno), Asia and Southeast Asia (eg, Wadjak, Zhoukoudian Upper Cave, and Niah Cave), the Near East (eg, Skhul and Djebel Qafzeh), and Australia (eg, Willandra Lakes). The first African fossil evidence for *H. sapiens* came in 1924 from Singa in the Sudan, with subsequent evidence coming from Border Cave and Klasies River Mouth in South Africa; Dar es Soltane in Morocco; and Dire-Dawa, Herto, and Omo-Kibish in Ethiopia. With the exception of the c.190 ka date for Omo-Kibish (McDougall et al., 2005) and the c.170 ka date for Herto (Clark et al., 2003) there is no firm evidence to suggest that any of the above sites is likely to be older than 150 ka, and most are probably younger than 100 ka.

Homo neanderthalensis

The next species for consideration in this time interval, *H. neanderthalensis* (King, 1864), was established for the partial skeleton recovered in 1856 from the Kleine Feldhofer Grotte in the part of the Düssel valley named after Joachim Neander. Excavations of the same sediments in 1997 and thereafter resulted in the recovery of fauna, artifacts, and some 80 hominin fragments from at least two hominin individuals were recovered. Discoveries made before 1856, such as the infant's cranium from Engis in 1828, and the partial cranium from Forbes' Quarry, Gibraltar, in 1848, were subsequently recognized as belonging to *H. neanderthalensis*. In the following half-century remains attributed to *H. neanderthalensis* were discovered at other European sites, including La Naulette and Spy in Belgium, Šipka in Moravia, Krapina in Croatia, and Malarnaud, La Chapelle-aux-Saints, Le Moustier (lower shelter), La Ferrassie, and La Quina, among others, in France. In 1924—6 the first *H. neanderthalensis* remains were found outside of Western Europe at Kiik-Koba in the Crimea, and thereafter came discoveries at Tabun cave on Mount Carmel in the Levant, at Teshik-Tash in central Asia. Further evidence was added after World War II, first from Shanidar in Iraq, then from Amud and Kebara in Israel, and from Dederiyeh in Syria. New fossiliferous localities continue to be discovered in Europe (eg, Saint-Césaire and Moula-Guercy in France, Zafarraya in Spain, Vindija in Croatia, and Lakonis in Greece) and Western Asia (eg, Mezmaiskaya and Denisova in Russia). To date, Neandertal remains have been found throughout much of Europe below 55°N, in the Near East. and in Western Asia, but no evidence has been found in North Africa.

The earliest fossils most researchers accept as *H. neanderthalensis* are from OIS 5 (ie, c.130 ka): beyond

that there is no consensus. For example, some (eg, Hublin, 2009) interpret the fossil evidence from Swanscombe (OIS 11, ie, c.425−375 ka) and the Sima de los Huesos (possibly as early as OIS 12, ie, c.475−425 ka) as showing enough Neandertal-like morphology to justify inclusion in *H. neanderthalensis*, whereas others see a distinction between these specimens, which they would include in *H. heidelbergensis*, and later "true" Neandertals they claim do not appear until OIS 6 (eg, Rosas et al., 2006).

Nuclear and mtDNA have been used to generate estimates of the date of divergence of *H. sapiens* and *H. neanderthalensis*. An estimate using mtDNA and based on an assumed divergence time of c.6−7 Ma for the modern human and chimpanzees/bonobo lineages suggests a coalescence age of 660 ± 140 ka (Green et al., 2008). Estimates of the divergence time of the ancestral modern human and Neandertal populations based on the nuclear genome range from 440 ka (this assumes an 8.3 Ma divergence date for chimpanzees/bonobos and modern humans) to 270 ka (assuming a later, 5.6 Ma, divergence date) (Green et al., 2010). The evidence of the timing of the split between modern humans and Neandertals suggest it was c.600 ka.

Homo erectus and *Homo heidelbergensis*

Both species were reviewed in earlier time intervals.

Homo floresiensis

The next species, *Homo floresiensis* (Brown et al., 2004), was established to accommodate LB1, a partial adult hominin skeleton, and LB2, an isolated left P_3, recovered in 2003 from the Liang Bua cave on the island of Flores in Indonesia. More material belonging to LB1 and evidence allocated to individuals LB4−9, including LB6, a partial skeleton lacking a cranium, was recovered in 2004 (Morwood et al., 2005). The hypodigm now includes close to 100 individually numbered specimens that are estimated to represent fewer than 10 individuals.

The taxon was immediately controversial for at least two reasons. First, its estimated geological age of between c.17 and c.74 ka (it is probably closer to the latter age) substantially overlapped with the estimated ages of evidence of the presence of modern humans in the region. Second, its discoverers and describers interpreted its small overall size (the stature of LB1 is estimated to be c.105 cm and its body mass to be roughly between 25 and 30 kg), small brain (c.420 cm^3), and primitive morphology as evidence of a novel endemically dwarfed *Homo* species. Initially it was suggested that *H. floresiensis* was a dwarfed *H. erectus*, but the burden of subsequent analyses suggests that it may be more closely related to a more primitive hominin such as *H. habilis sensu lato* (Tocheri et al., 2007; Argue et al., 2009; Brown and Maeda, 2009; Morwood and Jungers, 2009).

Denisovans

The final evidence to be considered in this time interval is based on the analysis of ancient DNA recovered from the distal phalanx of the fifth (little finger) digit of a hominin hand (Denisova 3) recovered from the c.48−30 ka layer 11 in Denisova Cave in the Altai Mountains in Russia. When mtDNA from the distal phalanx was compared with the mtDNA of 54 modern humans, one chimpanzee and one bonobo, six Neandertals, and a single fossil *H. sapiens* from Kostenki (Krause et al., 2010) it was concluded that it came from a hominin that, while distinct from both modern humans and Neandertals, shared a common ancestor with both species c.1.0 million years ago. Reich et al. (2010) sequenced the nuclear genome of the Denisova hominin phalanx and more mtDNA from a large-crowned maxillary molar (Denisova 8) found in the cave whose crown morphology is distinct from both modern humans and Neandertals. Meyer et al. (2015) recently published a high-coverage sequence from the same individual. Subsequently, a deciduous molar (Denisova 2) and another maxillary molar (Denisova 4) have been identified as Denisovans (Sawyer et al., 2015; Slon et al., 2015). The nuclear genome sequence showed that Denisovans and Neandertals split from each other after their common ancestor had separated from the line leading to modern humans, but confirmed that Denisovans and Neandertals split from each other after their common ancestor had separated from the lineage leading to modern humans. It also confirmed the hypothesis that Denisovans and Neandertals were distinct populations, because DNA recovered from different Neandertals across Europe was consistently more similar to one another than any was to the Denisovan DNA. One study of mitochondrial DNA of an individual from Sima de los Huesos (Meyer et al., 2014) has shown a closer affinity between the mtDNA of Denisovans and Sima de los Huesos than between Denisovans and Neandertals or modern humans. The implications of this finding remain to be tested with nuclear DNA data from Sima de los Huesos.

Evidence of Diversity

Any proposal for a hominin species other than modern humans in the 0.25 Ma to the present time interval that uses morphological evidence must demonstrate that the fossil evidence lies outside the envelope of the morphological variation documented for *H. sapiens*. And, if more than one set of fossil evidence meets that challenge, then the proposers must demonstrate that each set of fossil

evidence is distinctive enough to be referred to a separate species.

Those who claim that *H. neanderthalensis* is specifically distinct from *H. sapiens* recognize morphological autapomorphies that distinguish the former from both earlier (eg, *H. erectus* and *H. heidelbergensis*) and contemporary (ie, *H. sapiens*) Euro-Asian hominin taxa. These features are found in the cranium (eg, large, rounded discrete brow ridges, projecting mid-face, angled cheeks, small mastoid process, suprainiac fossa, and occipital bun), mandible (eg, long corpus, retro-molar space, and asymmetric mandibular notch), dentition (eg, large shovel-shaped incisors, distinctive occlusal morphology of molars and premolars, a high incidence of taurodontism), and in the postcranial skeleton (eg, long clavicle, teres minor groove extending onto the dorsal surface of the scapula, large infraspinous fossa, long, thin pubic ramus, and large joints). There are also reports that the ontogeny of *H. neanderthalensis* differs from that of modern humans (Tillier, 1982; Nelson and Thompson, 2005; Coqueugniot and Hublin, 2007; Ponce de León et al., 2008; Gunz et al., 2010; Smith et al., 2010).

The taxon *H. neanderthalensis* is currently the only extinct hominin for which ancient DNA evidence has been recovered from many individuals across several sites. The draft sequence of the Neandertal nuclear genome (Green et al., 2010), which focused on three individuals (Vi33.16, 25, and 26) from Vindija, was compared with smaller amounts of sequence data from Neandertal specimens from El Sidron, Kleine Feldhofer Grotte, and Mezmaiskaya, as well as the sequenced nuclear genomes of five modern humans. The results show that whereas the modern human sample from sub-Saharan Africa contained no evidence of Neandertal DNA, the three modern humans from outside of Africa showed similar, low (between 1% and 4%) amounts of DNA shared with Neandertals. These results are compatible with either a deep split within Africa between the population that gave rise to modern Africans and a second one that gave rise to present-day non-Africans plus Neandertals, or with the hypothesis that there was hybridization between Neandertals and modern humans soon after the latter left Africa, perhaps in Western Asia. In summary, the morphological and the genetic differences between modern humans and Neandertals are both consistent with a species-level distinction.

With respect to the alpha taxonomy of *H. floresiensis*, views are sharply polarized. The consensus is that if you take the hypodigm as a whole it is most parsimoniously interpreted as evidence of a novel endemically dwarfed premodern *Homo*, or early *Homo*, species. Less than a handful of researchers, literally, cling to the view that the "*H. floresiensis* hypodigm" samples an *H. sapiens* population—most likely related to the small-statured Rampasasa people who live on Flores today—all of which are afflicted by either an endocrine disorder (see Obendorf et al., 2008 and a rebuttal by Brown, 2012) or one or more of a range of syndromes that include microcephaly. Both explanations, a novel dwarfed early hominin species, or a pathological population of modern humans, are exotic, but those who espouse a pathological explanation for the individuals represented by LB1−15 need to explain what pathology results in a phenotype that resembles an early *Homo*-like cranial vault, primitive mandibular, dental, carpal, and pedal morphology, and a brain that, while very small, apparently has none of the morphological features associated with the majority of types of microcephaly (Vannucci et al., 2011). We subscribe to the interpretation that the fossil evidence from Liang Bua is a dwarfed early *Homo* species that is clearly phenotypically distinct from all of the other taxa in this time interval.

Differences between the ancient mtDNA and nuclear DNA extracted from the distal phalanx of the fifth (little finger) digit of a hominin hand, and the mtDNA extracted from a large-crowned maxillary molar, both found in Denisova Cave, and the DNA of modern humans and Neandertals, are consistent with the Denisovans and modern humans belonging to different species (Reich et al., 2011; Patterson et al., 2012; Prüfer et al., 2014). Denisovans and Neandertals were also likely to have been separate species given that DNA recovered from Neandertals across Europe was consistently more similar to one another than any was to the Denisovan DNA.

So within the time interval between 0.25 Ma to the present time, there seems sound evidence for hominin taxic diversity in the form of species-level differences among *H. sapiens*, *H. neanderthalensis*, *H. erectus*, and *H. floresiensis*. There is also less strong, but still potential, evidence for two more taxa, *H. heidelbergensis* and the Denisovans. It is also possible that the *H. heidelbergensis* hypodigm and the Denisovan DNA sample the same taxon (Meyer et al., 2014), especially if mtDNA results were to be confirmed by the results of future nuclear DNA analyses, but the substantial morphological and metric differences between one of the upper molars from Denisovan and equivalent teeth from the Sima de los Huesos cast doubt on that scenario.

DISCUSSION

The assessment of taxic diversity depends on generating hypotheses about the existence of hominin species and how long-lived they are (Fig. 2.1). Both types of proposal are bedeviled by sampling problems. Namely, how close are the available data to the type and scale of data one would need in order to generate reliable hypotheses about the presence and time span of each proposed hominin species?

Turning first to the realm of taxonomy, the criteria that should be used to determine if a newly discovered fossil sample falls outside the range of variation of an existing species are the same ones researchers should use when they determine if a newly discovered evidence about a living animal justifies the erection of a new species. They compare the newly discovered phenotype with museum collections that sample the species closest to it, and if the researchers are convinced the new specimen falls comfortably outside the range of variation of existing species, they have grounds for erecting a new species. The equivalent exercise involving the hominin fossil record would be to use the observed range of variation for the relevant variables of the reference taxon (eg, *Au. afarensis*) in the time interval occupied by the newly discovered fossils (eg, c.3.4 Ma) and if the newly discovered fossils fall comfortably outside that range of variation, then there are grounds for erecting a new fossil species. But while museum collections of most living animals comprise samples of complete specimens numbered in the hundreds, we do not have the equivalent of these comprehensive museum collections to estimate the parameters of the reference fossil hominin species, just the fossils that make up the hypodigms of those species. To go back to our hominin example, researchers have access to what in relative terms is a respectable sample of *Au. afarensis* from Hadar, with important but much smaller samples from other sites, but that becomes a much smaller sample when you restrict it to the parts of the hypodigm known from c.3.4 Ma. But even if one relaxes the time constraint, and considers the regions of the skeleton (eg, dentition and mandible) that are best represented in the *Au. afarensis* hypodigm, we are still talking about sample sizes that would be considered unacceptably low in studies of extant primates. If the new fossil evidence happens to preserve an anatomical region in which the ratio of inter- to intraspecific variation is favorable, and if the specimens are relatively complete, it is possible to demonstrate taxic diversity even with relatively small sample sizes. Indeed, there are several instances in the hominin fossil record where just one new fossil (eg, OH 7) is so different from the fossil evidence of a synchronic species (eg, OH 5, the type specimen of *P. boisei*) that the case for taxonomic distinctiveness is obvious. But not all claims for new hominin taxa are as securely based as this example (see Smith, 2005).

How can the situation be improved? The obvious solution is to find additional hominin fossil evidence from new and existing sites and localities, and then provide, in a timely fashion, detailed information about the new evidence. This will serve to expand our knowledge of existing fossil hominin taxa. But while we await the assembly of these much larger hypodigms, is there anything else we can do? One strategy is to expand our understanding of variation within closely related extant taxa and apply any lessons learned to interpreting the hominin fossil record. Comparative studies that collect data for a particular anatomical region from large samples of the great apes, such as the studies of dental morphology by Uchida (2004) and Pilbrow (2010), are especially helpful because they allow us to conduct the thought experiment of imagining what variation in a large sample of an early hominin species might look like. Another strategy is to look at patterns of inter- and intraspecific variation within and among the extant taxa most closely related to fossil hominins. If there are any common patterns, and if we make the reasonable working assumption that the hominin clade shares the same pattern (ie, using the principle of the phylogenetic bracket, see Witmer, 1995), parsimony suggests the observed pattern should also apply to fossil hominin taxa. Sound comparative evidence about inter- and intraspecific variation could then be used to generate additional criteria to help researchers make judgments about the taxonomic significance of morphological differences between small samples of fossil hominins (eg, Wood, 1975; Wood et al., 1991). But until we have larger hypodigms for fossil hominin taxa, the procedures traditionally used in paleoanthropology are likely to lead to the "over-reporting" of new taxa.

The assessment of taxic diversity also depends on the ability to determine how long-lived taxa are. Studies that looked at the time span of mammalian taxa in the Cenozoic resulted in estimates of the median duration of a species that range from 1.7 Ma (Foote and Raup, 1996) to 0.6 Ma (Barnosky et al., 2011). Two early hominin species, *Au. afarensis* and *P. boisei*, have a good fossil record with well-dated samples from several sites, and their hypodigms span c.0.7 and c.1.0 Ma, respectively. Taken overall these data suggest it is a reasonable working hypothesis to assume that the median duration of an early hominin species was in the order of one million years, plus or minus 0.25 Ma years.

We can also work with the data we have for each hominin species. To assign species, site samples, and individual fossils to time intervals, we used conservative versions of the FAD and LAD of each species based on their published ages (Table 2.1). We also assembled a second version that, where applicable, incorporates the published error of the age of the nearest underlying dated horizon in the case of the FAD, and the published error of the age of the nearest overlying dated horizon in the case of the LAD (Table 2.1; for details see Appendix A in Wood and Boyle, 2016). For various reasons even this observed FAD of a taxon is almost certainly later than the time the taxon actually originated in, or migrated into, that region, just as the equivalent observed LAD of a taxon is almost certainly earlier than the time the taxon became extinct or emigrated from that region. Just how much earlier than the observed FAD the actual origination or migration occurred,

and just how much later than the observed LAD of a taxon the actual extinction or emigration occurred, is determined by many factors. These include technical considerations such as dating error, but a much more potent factor is the nature of the relevant mammalian fossil record before and after the current observed FAD and LAD. The problem is the old adage "absence of evidence is not evidence of absence"—in other words it is a sampling problem. At most sites early hominins are such a rare component of the mammalian faunal record (c.1–2%) that researchers need to find a substantial number of nonhominin mammalian fossils (at least several hundred) without finding *any* evidence of a particular hominin species before it can be reasonably assumed any hominin species was not part of the faunal assemblage being sampled. And at sites such as Koobi Fora where there is a major break in sedimentation that spans several hundred thousand years prior to the FAD of several hominin species (ie, there is no fossil record during that time) we have little basis for concluding there were no hominins prior to their FAD at that site (Bobe and Leakey, 2009). We know even less about the time span of the early hominin species that are presently found only at Southern African sites.

There are uncertainties about the temporal span of all of the fossil hominin taxa we reviewed above, especially those with small hypodigms sampled at just one or two sites. But what we can say about these uncertainties is that because it is impossible for a FAD to occur before a species actually originated, or for a LAD to occur after a species actually went extinct, any species recognized in the hominin fossil record is likely to extend into more, rather than fewer, time intervals. So, *all* of the species we reviewed, especially the ones with modestly sized hypodigms, will almost certainly have had longer temporal spans than the ones we used, leading to the systematic underestimation of hominin taxic diversity.

CONCLUSIONS

We summarize our assessment of the strength of the existing evidence for species distinctions in the form of pairwise comparisons of species, or species equivalents, for each of the time intervals (Table 2.2). In each time interval we list the species, or species equivalents, in order of their proposal or discovery and score the case for each of the comparisons into one of three confidence categories: high, medium, or low. It will be obvious, but in any event we want to emphasize the obvious, that these are subjective assessments others can challenge, but at least these proposals for hominin taxonomic diversity are "on the table" for debate. As can be seen from Table 2.2, apart from the period prior to 5 Ma, in all of the time intervals we sampled there is at least one example of diversity that enjoys what we judge to be a high level of confidence. These examples

TABLE 2.2 Assessment of the Strength of the Evidence for Taxic Diversity Within the Time Intervals Described in the Text

7–5 Ma
High Confidence
N/A
Moderate Confidence
Orrorin tugenensis vs *Sahelanthropus tchadensis*
Orrorin tugenensis vs *Ardipithecus kadabba*
Sahelanthropus tchadensis vs *Ardipithecus kadabba*
Low Confidence
N/A
5–4 Ma
High Confidence
Ardipithecus ramidus vs *Australopithecus anamensis*
Moderate Confidence
N/A
Low Confidence
N/A
4–3 Ma
High Confidence
Australopithecus afarensis vs Burtele foot
Moderate Confidence
Australopithecus afarensis vs *Kenyanthropus platyops*
Low Confidence
Australopithecus afarensis vs *Australopithecus bahrelghazali*
Australopithecus afarensis vs *Australopithecus deyiremeda*
Kenyanthropus platyops vs *Australopithecus deyiremeda*
Kenyanthropus platyops vs Burtele foot
Burtele foot vs *Australopithecus deyiremeda*
3.0–2.5 Ma
High Confidence
Australopithecus africanus vs *Paranthropus aethiopicus*
Australopithecus africanus vs LD 350-1
Paranthropus aethiopicus vs LD 350-1
Moderate Confidence
N/A
Low Confidence
N/A

Continued

TABLE 2.2 Assessment of the Strength of the Evidence for Taxic Diversity Within the Time Intervals Described in the Text—cont'd

2.5–2.0 Ma
High Confidence
Australopithecus africanus vs *Paranthropus boisei*
Paranthropus boisei vs *Homo habilis sensu lato*
Australopithecus garhi vs *Homo habilis sensu lato*
Moderate Confidence
Australopithecus africanus vs *Homo habilis sensu lato*
Australopithecus africanus vs *Australopithecus garhi*
Paranthropus boisei vs *Australopithecus garhi*
Homo habilis sensu stricto vs *Homo rudolfensis*
Low Confidence
N/A
2.0–1.5 Ma
High Confidence
Homo erectus vs *Paranthropus robustus*
Homo erectus vs *Paranthropus boisei*
Homo erectus vs *Australopithecus sediba*
Paranthropus robustus vs *Homo habilis sensu lato*
Paranthropus robustus vs *Australopithecus sediba*
Paranthropus boisei vs *Homo habilis sensu lato*
Paranthropus boisei vs *Australopithecus sediba*
Homo habilis sensu lato vs *Australopithecus sediba*
Moderate Confidence
H.omo erectus vs *Homo habilis sensu lato*
Paranthropus robustus vs *Paranthropus boisei*
Homo habilis sensu stricto vs *Homo rudolfensis*
Low Confidence
Homo erectus vs *Homo ergaster*
Homo erectus vs *Homo georgicus*
1.5–1.0 Ma
High Confidence
Homo erectus vs *Paranthropus robustus*
Homo erectus vs *Paranthropus boisei*
Paranthropus robustus vs *Homo habilis sensu lato*
Paranthropus robustus vs *Homo antecessor*[a]
Paranthropus boisei vs *Homo antecessor*[a]
Homo habilis sensu lato vs *Homo antecessor*[a]
Moderate Confidence
Homo erectus vs *Homo habilis sensu lato*
Paranthropus robustus vs *Paranthropus boisei*

Continued

TABLE 2.2 Assessment of the Strength of the Evidence for Taxic Diversity Within the Time Intervals Described in the Text—cont'd

Low Confidence
Homo erectus vs *Homo ergaster*
Homo erectus vs *Homo antecessor*
1.0-0.25 Ma
High Confidence
Homo erectus vs *Homo heidelbergensis*
Homo erectus vs *Homo rhodesiensis*
Homo erectus vs *Homo helmei*
Homo erectus vs Sima de los Huesos
Homo heidelbergensis vs Sima de los Huesos
Homo rhodesiensis vs Sima de los Huesos
Homo helmei vs Sima de los Huesos
Moderate Confidence
N/A
Low Confidence
Homo heidelbergensis vs *Homo rhodesiensis*
Homo heidelbergensis vs *Homo helmei*
0.25 Ma–present
High Confidence
Homo sapiens vs *Homo neanderthalensis*
Homo sapiens vs *Homo erectus*
Homo sapiens vs *Homo heidelbergensis*
Homo sapiens vs *Homo floresiensis*
Homo sapiens vs Denisovans
Homo erectus vs *Homo heidelbergensis*
Homo erectus vs *Homo floresiensis*
Homo neanderthalensis vs *Homo erectus*
Homo neanderthalensis vs *Homo floresiensis*
Homo heidelbergensis vs *Homo floresiensis*
Moderate Confidence
Homo neanderthalensis vs Denisovans
Homo erectus vs Denisovans
Low Confidence
Homo neanderthalensis vs *Homo heidelbergensis*
Homo heidelbergensis vs Denisovans

For each of the nine time intervals relevant to the hominin fossil record, we assess the strength of the evidence for taxic diversity among hominin species by allocating each pairwise comparison to one of three categories of confidence, high, moderate or low.

[a]*If the partial mandible (ATE9-1) from the Sima del Elefante does not belong to* Homo antecessor, *then these "high confidence" pairwise comparisons fall away.*

are likely to grow as hypodigms expand and new sites extend the time ranges of the existing species. There is also the potential for finding fossil evidence of additional species such as *Homo naledi* (Berger et al., 2015). Our very preliminary assessment of the evidence recovered from the Dinaledi chamber of the Rising Star system suggests that the claim that this is a new species needs to be taken seriously. But even if the discoveries in the Dinaledi Chamber add to the evidence for taxonomic diversity, until researchers can determine its age (Dirks et al., 2015) we will not know which time interval, or intervals, would be affected by this new evidence.

As for the future, researchers who find new fossil evidence that lies outside the envelope of the hypodigms of closely related species should at least convince themselves that the new material is unlikely to be sampled from the species from which the existing sample (ie, hypodigm) has been drawn. That is a very different investigation from the usual one that decides whether the new fossils are outside the range of the hypodigms of existing hominin species from approximately the same time period. We must guard against the tendency in all of us to "focus on the strength or extremeness of the available evidence" and to have "insufficient regard for its weight or credence" (Griffin and Tversky, 1992, p. 411). This tendency may explain why people in general, and perhaps paleoanthropologists in particular, are "often more confident in their judgments than is warranted by the facts" (Griffin and Tversky, 1992, p. 411). Devising a formal strategy to take account of this tendency for overconfidence is a challenge that faces all researchers involved in fossil discovery.

What this evidence for taxic diversity means for lineage diversity within the hominin clade is outside the scope of this review, but while lineage diversity cannot exist without taxonomic diversity, taxonomic diversity does not always mean there is lineage diversity. For example, although we suggest there is evidence of a species-level distinction between *Au. anamensis* and *Au. afarensis*, and between *P. aethiopicus* and *P. boisei*, there is also evidence that at least one of these pairs of taxa (Kimbel et al., 2006) belong to the same lineage. Also, we are not as convinced as some of our colleagues that current phylogenetic hypotheses are sound enough to make convincing inferences about lineage diversity.

It is evident from this review that proposals to recognize new hominin taxa are not equally convincing. However, our interpretation of the fossil evidence suggests that for at least the past four and a half million years there is compelling evidence for taxic diversity within the hominin clade.

ACKNOWLEDGMENTS

We would like to thank Andrew Barr, Aida Gómez-Robles, Bill Kimbel, and Richard Smith for their insightful comments on an earlier version, and Brenda Bradley for her help with interpreting the DNA literature. Needless to say, any remaining errors are our responsibility, not theirs. Bernard Wood would like to thank the Provost of George Washington University for his continuing support for the George Washington University Professorship of Human Origins and via the George Washington Signature Program for his support of CASHP. Eve Boyle was supported by the NSF-IGERT DGE-0801634 and is now supported by a GW Provost's Diversity Fellowship.

Sponsorship: GW Provost's Signature Program Funding (award to BW), GW Provost's Diversity Graduate Fellowship (award to EB)

REFERENCES

Ackermann, R.R., Smith, R.J., 2007. The macroevolution of our ancient lineage: what we know (or think we know) about early hominin diversity. Evolutionary Biology 34, 72–85.

Ahern, J.C., 2005. Foramen magnum position variation in *Pan troglodytes*, Plio-Pleistocene hominids, and recent *Homo sapiens*: implications for recognizing the earliest hominids. American Journal of Physical Anthropology 127 (3), 267–276.

Almécija, S., Moyà-Solà, S., Alba, D.M., 2010. Early origin for human-like precision grasping: a comparative study of pollical distal phalanges in fossil hominins. Public Library of Science 5, e11727.

Almécija, S., Tallman, M., Alba, D.M., et al., 2013. The femur of *Orrorin tugenensis* exhibits morphometric affinities with both Miocene apes and later hominins. Nature Communications 4, 2888.

Almécija, S., Smaers, J.B., Jungers, W.L., 2015. The evolution of human and ape hand proportions. Nature Communications 6, 7717.

Arambourg, C., Coppens, Y., 1968. Découverte d'un australopithecien nouveau dans les Gisements de L'Omo (Ethiopie). South African Journal of Science 64, 58–59.

Argue, D., Morwood, M.J., Sutikna, T., et al., 2009. *Homo floresiensis*: a cladistic analysis. Journal of Human Evolution 57, 623–639.

Arsuaga, J.L., Martinez, I., Garcia, A., et al., 1997. The Sima de los Huesos crania (Sierra de Atapuerca, Spain). A comparative study. Journal of Human Evolution 33, 219–281.

Asfaw, B., White, T., Lovejoy, O., et al., 1999. *Australopithecus garhi*: a new species of early hominid from Ethiopia. Science 284, 629–635.

Barnosky, A.D., Matzke, N., Tomiya, S., et al., 2011. Has the Earth's sixth mass extinction already arrived? Nature 471, 51–57.

Berger, L.R., de Ruiter, D.J., Churchill, S.E., et al., 2010. *Australopithecus sediba*: a new species of *Homo*-like australopith from South Africa. Science 328, 195–204.

Berger, L.R., Hawks, J., de Ruiter, D.J., et al., 2015. *Homo naledi*, a new species of the genus *Homo* from the Dinaledi Chamber, South Africa. eLife 4, e09560.

Bermúdez de Castro, J.M., Arsuaga, J.L., Carbonell, E., et al., 1997. A hominid from the lower Pleistocene of Atapuerca, Spain: possible ancestor to Neandertals and modern humans. Science 276, 1392–1395.

Bermudez de Castro, J.M., Martinon-Torres, M., Gómez-Robles, A., et al., 2011. Early Pleistocene human mandible from Sima del Elefante (TE) cave site in Sierra de Atapuerca (Spain): a comparative morphological study. Journal of Human Evolution 61, 12–25.

Bermúdez de Castro, J.M., Martinón-Torres, M., Lozano, M., et al., 2004. Paleodemography of the Atapuerca: Sima De Los Huesos Hominin Sample: A Revision and New Approaches to the Paleodemography of the European Middle Pleistocene Population. Journal of Anthropological Research 60, 5–26.

Black, D., 1927. On a lower molar hominid tooth from Chou-kou-tien deposit. Palaeontologica Sinica 7, 1−28.

Bobe, R., Leakey, M.G., 2009. Ecology of Plio-Pleistocene mammals in the Omo-Turkana basin and the emergence of *Homo*. In: Grine, F.E., Fleagle, J.G., Leakey, R.E. (Eds.), The First Humans − Origin and Early Evolution of the Genus *Homo*. Vertebrate Paleobiology and Paleoanthropology. Springer, Dordrecht, pp. 173−184.

Bradley, B.J., 2008. Reconstructing phylogenies and phenotypes: a molecular view of human evolution. Journal of Anatomy 212, 337−353.

Broom, R., Robinson, J.T., 1950. Man contemporaneous with the Swartkrans ape-man. American Journal of Physical Anthropology 8, 151−156.

Broom, R., 1938. The Pleistocene anthropoid apes of South Africa. Nature 142, 377−379.

Brown, P., Maeda, T., 2009. Liang Bua *Homo floresiensis* mandibles and mandibular teeth: a contribution to the comparative morphology of a hominin species. Journal of Human Evolution 57, 571−596.

Brown, B., Brown, F.H., Walker, A., 2001. New hominids from the Lake Turkana Basin, Kenya. Journal of Human Evolution 41, 29−44.

Brown, P., Sutikna, T., Morwood, M.J., et al., 2004. A new small-bodied hominin from the Late Pleistocene of Flores, Indonesia. Nature 431, 1055−1061.

Brown, P., 2012. LB1 and LB6 *Homo floresiensis* are not modern human (*Homo sapiens*) cretins. Journal of Human Evolution 62, 201−224.

Brunet, M., Beauvilain, A., Coppens, Y., et al., 1995. The first australopithecine 2,500 kilometers west of the Rift Valley (Chad). Nature 376, 273−275.

Brunet, M., Beauvilain, A., Coppens, Y., et al., 1996. *Australopithecus bahrelghazali*, une nouvelle espèce d'Hominidé ancien de la région de Koro Toro (Tchad). Comptes Rendus de l'Académie des Sciences 322, 907−913.

Brunet, M., Guy, F., Pilbeam, D., et al., 2002. A new hominid from the Upper Miocene of Chad, Central Africa. Nature 418, 145−151.

Brunet, M., Guy, F., Pilbeam, D., et al., 2005. New material of the earliest hominid from the Upper Miocene of Chad. Nature 434, 752−755.

Carbonell, E., Bermúdez de Castro, J.M., Arsuaga, J.L., et al., 2005. An Early Pleistocene hominin mandible from Atapuerca-TD6, Spain. Proceedings of the National Academy of Sciences of the United States of America 102, 5674−5678.

Carbonell, E., Bermúdez de Castro, J.M., Parés, J.M., et al., 2008. The first hominin of Europe. Nature 452, 465−469.

Carlson, K.J., Stout, D., Jashashvili, T., et al., 2011. The endocast of MH1, *Australopithecus sediba*. Science 333, 1402−1407.

Chamberlain, A.T., Wood, B.A., 1987. Early hominid phylogeny. Journal of Human Evolution 16, 119−133.

Clark, J.D., Beyene, Y., WoldeGabriel, G., et al., 2003. Stratigraphic, chronological and behavioural contexts of Pleistocene *Homo sapiens* from middle Awash, Ethiopia. Nature 423, 747−752.

Clarke, R.J., 1988. A new *Australopithecus* cranium from Sterkfontein and its bearing on the ancestry of *Paranthropus*. In: Grine, F.E. (Ed.), Evolutionary History of the "Robust" Australopithecines. Evolutionary History of the "Robust" Australopithecines. Aldine de Gruyter, New York, pp. 285−292.

Clarke, R., 1999. Discovery of complete arm and hand of the 3.3 million-year-old *Australopithecus* skeleton from Sterkfontein. South African Journal of Science 95, 477−480.

Clarke, R.J., 2008. Latest information on Sterkfontein's *Australopithecus* skeleton and a new look at *Australopithecus*. South African Journal of Science 104, 443−449.

Consortium TCSA, 2005. Initial sequence of the chimpanzee genome and comparison with the human genome. Nature 437, 69−87.

Coqueugniot, H., Hublin, J., 2007. Endocranial volume and brain growth in immature Neandertals. Periodicum Biologorum 109, 379−385.

Dart, R., 1925. *Australopithecus africanus*: the man-ape from South Africa. Nature 115, 195−199.

Dart, R.A., 1948. The Makapansgat proto-human *Australopithecus prometheus*. American Journal of Physical Anthropology 6, 259−284.

Dean, D., Hublin, J.-J., Holloway, R., et al., 1998. On the phylogenetic position of the pre-Neandertal specimen from Reilingen, Germany. Journal of Human Evolution 34, 485−508.

Diogo, R., Wood, B., 2011. Soft-tissue anatomy of the primates: phylogenetic analyses based on the muscles of the head, neck, pectoral region and upper limb, with notes on the evolution of these muscles. Journal of Anatomy 219, 273−359.

Dirks, P.H.G.M., Berger, L.R., Roberts, E.M., et al., 2015. Geological and taphonomic context for the new hominin species *Homo naledi* from the Dinaledi Chamber, South Africa. eLife 4, e09561.

Drapeau, M.S.M., 2012. Forelimb adaptations in *Australopithecus afarensis*. In: Reynolds, S.C., Gallagher, A. (Eds.), African Genesis. Perspectives on Hominin Evolution. Cambridge University Press, Cambridge, pp. 223−247.

Dreyer, T.F., 1935. A human skull from Florisbad, Orange Free State, with a note on the endocranial cast, by C.U. Ariëns Kappers. Proceedings of the Royal Academy of Sciences of Amsterdam 38, 119−128.

Dubois, E., 1893. Palaeontologische onderzoekingen op Java. Verslag Mijnwezen (Batavia) 10, 10−14.

Emonet, E.-G., Andossa, L., Mackaye, H.T., et al., 2014. Subocclusal dental morphology of *Sahelanthropus tchadensis* and the evolution of teeth in hominins. American Journal of Physical Anthropology 153 (1), 116−123.

Foote, M., Raup, D.M., 1996. Fossil preservation and the stratigraphic ranges of taxa. Paleobiology 22, 121−140.

Gabounia, L., de Lumley, M.-A., Vekua, A., et al., 2002. Découverte d'un nouvel hominidé à Dmanissi (Transcaucasie, Géorgie). Comptes Rendus Palevol 1, 243−253.

Galik, K., Senut, B., Pickford, M., et al., 2004. External and internal morphology of the BAR 1002'00 *Orrorin tugenensis* femur. Science 305, 1450−1453.

Gibbs, S., Collard, M., Wood, B.A., 2002. Soft-tissue anatomy of the extant hominoids: a review and phylogenetic analysis. Journal of Anatomy 200, 3−49.

Gómez-Robles, A., Bermúdez de Castro, J.M., Martinon-Torres, M., et al., 2015. A geometric morphometric analysis of hominin lower molars. Evolutionary implications and overview of postcanine dental variation. Journal of Human Evolution 82, 34−50.

Gordon, A.D., Green, D.J., Richmond, B.R., 2008. Strong postcranial size dimorphism in *Australopithecus afarensis*: results from two new resampling methods for multivariate data sets with missing data. American Journal of Physical Anthropology 135, 311−328.

Grabowski, M., Hatala, K.G., Jungers, W.L., et al., 2015. Body mass estimates of hominin fossils and the evolution of human body size. Journal of Human Evolution 85, 75−93.

Granger, D.E., Gibbon, R.J., Kuman, K., et al., 2015. New cosmogenic burial ages for Sterkfontein Member 2 *Australopithecus* and Member 5 Oldowan. Nature 522, 85–88.

Green, R.E., Malaspinas, A.S., Krause, J., et al., 2008. A complete Neandertal mitochondrial genome sequence determined by high-throughput sequencing. Cell 134, 416–426.

Green, R.E., Krause, J., Briggs, A.W., et al., 2010. A draft sequence of the Neandertal genome. Science 328, 710–722.

Griffin, D., Tversky, A., 1992. The weighing of evidence and the determinants of confidence. Cognitive Psychology 24, 411–435.

Groves, C.P., Mazák, V., 1975. An approach to the taxonomy of the Hominidae: gracile Villafranchian hominids of Africa. Casopis pro Mineralogii a Geologii 20, 225–247.

Groves, C.P., 1989. A Theory of Human and Primate Evolution. Clarendon Press, Oxford.

Gunz, P., Neubauer, S., Maureille, B., et al., 2010. Brain development after birth differs between Neanderthals and modern humans. Current Biology 20 (21), R921–R922.

Guy, F., Lieberman, D.E., Pilbeam, D., et al., 2005. Morphological affinities of the *Sahelanthropus tchadensis* (Late Miocene hominid from Chad) cranium. Proceedings of the National Academy of Sciences of the United States of America 102, 18836–18841.

Guy, F., Mackaye, H.-T., Likius, A., et al., 2008. Symphyseal shape variation in extant and fossil hominoids, and the symphysis of *Australopithecus bahrelghazali*. Journal of Human Evolution 55, 37–47.

Haile-Selassie, Y., Suwa, G., White, T.D., 2004. Late Miocene teeth from Middle Awash, Ethiopia, and early hominid dental evolution. Science 303, 1503–1505.

Haile-Selassie, Y., Suwa, G., White, T., 2009. Hominidae. In: Haile-Selassie, Y., WoldeGabriel, G. (Eds.), *Ardipithecus kadabba* Late Miocene Evidence From the Middle Awash, Ethiopia. University of California Press, Berkeley, pp. 159–236.

Haile-Selassie, Y., Latimer, B., Alene, M., et al., 2010a. An early *Australopithecus afarensis* postcranium from Woranso-Mille, Ethiopia. Proceedings of the National Academy of Sciences of the United States of America 107, 12121–12126.

Haile-Selassie, Y., Saylor, B., Deino, A., et al., 2010b. New hominid fossils from Woranso-Mille (Central Afar, Ethiopia) and taxonomy of early *Australopithecus*. American Journal of Physical Anthropology 141, 406–417.

Haile-Selassie, Y., Saylor, B.Z., Deino, A., et al., 2012. A new hominin foot from Ethiopia shows multiple Pliocene bipedal adaptations. Nature 483, 565–569.

Haile-Selassie, Y., Gibert, L., Melillo, S.M., et al., 2015. New species from Ethiopia further expands Middle Pliocene hominin diversity. Nature 521, 483–488.

Haile-Selassie, Y., 2001. Late Miocene hominids from the Middle Awash, Ethiopia. Nature 412, 178–181.

Hublin, J.J., 2009. The origin of Neandertals. Proceedings of the National Academy of Sciences of the United States of America 106, 16022–16027.

Hunt, K.D., 2003. The single species hypothesis: truly dead and pushing up bushes, or still twitching and ripe for resuscitation? Human Biology 75, 485–502.

I.C.Z.N, 1999. Opinion 1941: *Australopithecus afarensis* Johanson, 1978 (Mammalia, Primates): specific name conserved. The Bulletin of Zoological Nomenclature 56, 223–224.

Johanson, D.C., Taieb, M., Coppens, Y., et al., 1978. Expedition internationale de l'Afar Ethiopie (4m et 5e campagnes 1975–1977): nouvelle decouvertes d'Hominides et decouvertes d'industries lithiques Pliocenes a Hadar. Comptes Rendus de l'Académie des Sciences 287, 237–240.

Kaifu, Y., Aziz, F., Indriati, E., et al., 2008. Cranial morphology of Javanese *Homo erectus*: new evidence for continuous evolution, specialization, and terminal extinction. Journal of Human Evolution 55, 551–580.

Kimbel, W.H., Delezene, L.K., 2009. "'Lucy'" redux: a review of research on *Australopithecus afarensis*. American Journal of Physical Anthropology 140, 2–48.

Kimbel, W.H., White, T.D., Johanson, D.C., 1984. Cranial morphology of *Australopithecus afarensis*: a comparative study based on a composite reconstruction of the adult skull. American Journal of Physical Anthropology 64, 337–388.

Kimbel, W., Rak, Y., Johanson, D.C., 2004. The Skull of *Australopithecus afarensis*. Oxford University Press, New York.

Kimbel, W.H., Lockwood, C.A., Ward, C.V., et al., 2006. Was *Australopithecus anamensis* ancestral to *A. afarensis*? A case of anagenesis in the hominin fossil record. Journal of Human Evolution 51, 134–152.

King, W., 1864. The reputed fossil man of the Neanderthal. Quarterly Journal of Science 1, 88–97.

Kivell, T.L., Kibii, J.M., Churchill, S.E., et al., 2011. *Australopithecus sediba* hand demonstrates mosaic evolution of locomotor and manipulative abilities. Science 333, 1411–1417.

Krause, J., Fu, Q., Good, J.M., et al., 2010. The complete mitochondrial DNA genome of an unknown hominin from southern Siberia. Nature 464, 894–897.

Langergraber, K.E., Prüfer, K., Rowney, C., et al., 2012. Generation times in wild chimpanzees and gorillas suggest earlier divergence times in great ape and human evolution. Proceedings of the National Academy of Sciences of the United States of America 109, 15716–15721.

Le Gros Clark, W.E., 1955. The Fossil Evidence for Human Evolution: An Introduction to the Study of Paleoanthropology. University of Chicago Press, Chicago.

Le Gros Clark, W.E., 1964. The Fossil Evidence for Human Evolution: An Introduction to the Study of Paleoanthropology, second ed. University of Chicago Press, Chicago.

Leakey, L.S.B., Tobias, P.V., Napier, J., 1964. A new species of the genus *Homo* from Olduvai Gorge. Nature 202, 7–9.

Leakey, M.G., Feibel, C.S., McDougall, I., et al., 1995. New four-million-year-old hominid species from Kanapoi and Allia Bay, Kenya. Nature 376, 565–571.

Leakey, M.G., Feibel, C.S., McDougall, I., et al., 1998. New specimens and confirmation of an early age for *Australopithecus anamensis*. Nature 393, 62–66.

Leakey, M.G., Spoor, F., Brown, F.H., et al., 2001. New hominin genus from eastern Africa shows diverse middle Pliocene lineages. Nature 410, 433–440.

Leakey, M.G., Spoor, F., Dean, M.C., et al., 2012. New fossils from Koobi Fora in northern Kenya confirm taxonomic diversity in early *Homo*. Nature 488, 201–204.

Leakey, L.S.B., 1959. A new fossil skull from Olduvai. Nature 184, 491–493.

Leakey, R.E.F., Walker, A.C., 1976. *Australopithecus*, *Homo erectus* and the single species hypothesis. Nature 261, 572–574.

Lebatard, A.E., Bourlès, D.L., Duringer, P., et al., 2008. Cosmogenic nuclide dating of *Sahelanthropus tchadensis* and *Australopithecus bahrelghazali*: Mio-Pliocene hominids from Chad. Proceedings of the National Academy of Sciences of the United States of America 105, 3226–3231.

Linnaeus, C., 1758. Systema Naturae. Laurentii Salvii, Stockholm.

Locke, D.P., Hillier, L.W., Warren, W.C., et al., 2011. Comparative and demographic analysis of orangutan genomes. Nature 469, 529–533.

Lockwood, C.A., Tobias, P.V., 2002. Morphology and affinities of new hominin cranial remains from Member 4 of the Sterkfontein Formation, Gauteng Province, South Africa. Journal of Human Evolution 42, 389–450.

Lockwood, C.A., Kimbel, W.H., Lynch, J.M., 2004. Morphometrics and hominioid phylogeny: support for a chimpanzee-human clade and differentiation among great ape subspecies. Proceedings of the National Academy of Sciences of the United States of America 101, 4356–4360.

Lordkipanidze, D., Ponce de León, M.S., Margvelashvili, A., et al., 2013. A complete skull from Dmanisi, Georgia, and the evolutionary biology of early *Homo*. Science 342, 326–331.

Lovejoy, C.O., Suwa, G., Simpson, S.W., et al., 2009. The great divides: *Ardipithecus ramidus* reveals the postcrania of our last common ancestors with African apes. Science 326, 73–106.

Manzi, G., Mallegni, F., Ascenzi, A., 2001. A cranium for the earliest Europeans: Phylogenetic position of the hominid from Ceprano, Italy. Proceedings of the National Academy of Sciences of the United States of America 98, 10011–10016.

Mayr, E., 1944. On the concepts and terminology of vertical subspecies and species. National Research Council Committee on Common Problems of Genetics, Paleontology, and Systematics Bulletin 2, 11–16.

Mayr, E., 1950. Taxonomic categories in fossil hominids. Cold Spring Harbor Symposia on Quantitative Biology 15, 109–118.

McDougall, I., Brown, F.H., Fleagle, J.G., 2005. Stratigraphic placement and age of modern humans from Kibish, Ethiopia. Nature 433, 733–736.

Meyer, M., Fu, Q., Aximu-Petri, A., et al., 2014. A mitochondrial genome sequence of a hominin from Sima de los Huesos. Nature 505, 403–406.

Meyer, M., Kircher, M., Gansange, M.-M., et al., 2015. A high-coverage genome sequence from an archaic Denisovan individual. Science 338, 222–226.

Morwood, M.J., Jungers, W.L., 2009. Conclusions: implications of the Liang Bua excavations for hominin evolution and biogeography. Journal of Human Evolution 57, 640–648.

Morwood, M.J., Brown, P., Jatmiko, et al., 2005. Further evidence for small-bodied hominins from the Late Pleistocene of Flores, Indonesia. Nature 437, 1012–1017.

Mounier, A., Marchal, F., Condemi, S., 2009. Is *Homo heidelbergensis* a distinct species? New insight on the Mauer mandible. Journal of Human Evolution 56, 219–246.

Nelson, A.J., Thompson, J.L., 2005. In: Ullrich, H. (Ed.), The Neandertal Adolescent Le Moustier. Staatliche Museen zu Berlin, Berlin, pp. 328–338.

Obendorf, P.J., Oxnard, C.E., Kefford, B.J., 2008. Are the small human-like fossils found on Flores human endemic cretins? Proceedings of the Royal Society B 275, 1287–1296.

Ohman, J.C., Lovejoy, C.O., White, T., 2005. Questions about *Orrorin tugenensis*. Science 307, 845.

Olson, T.R., 1981. Basicranial morphology of the extant hominoids and Pliocene hominids : the new material from the Hadar Formation, Ethiopia and its significance in early human evolution and taxonomy. In: Stringer, C.B. (Ed.), Aspects of Human Evolution. Taylor & Francis, London, pp. 99–128.

Olson, T.R., 1985a. Cranial morphology and systematics of the Hadar formation hominids and *Australopithecus africanus*. In: Delson, E. (Ed.), Ancestors: The Hard Evidence. Alan R. Liss, Inc., New York, pp. 102–119.

Olson, T.R., 1985b. Taxonomic affinities of the immature hominid crania from Hadar and Taung. Nature 316, 539–540.

Partridge, T.C., Granger, D.E., Caffee, D.E., et al., 2003. Lower Pliocene hominid remains from Sterkfontein. Science 300, 607–612.

Patterson, B., Howells, W.W., 1967. Hominid humeral fragment from early Pleistocene of northwest Kenya. Science 156, 64–66.

Patterson, N., Moorjani, P., Luo, Y., et al., 2012. Ancient admixture in human history. Genetics 192, 1065–1093.

Pickford, M., Senut, B., Gommery, D., et al., 2002. Bipedalism in *Orrorin tugenensis* revealed by its femora. Comptes Rendus Palevol 1, 1–13.

Pilbrow, V., 2010. Dental and phylogeographic patterns of variation in gorillas. Journal of Human Evolution 59, 16–34.

Ponce de León, M.S., Golovanova, L., Doronichev, V., et al., 2008. Neanderthal brain size at birth provides insights into the evolution of human life history. Proceedings of the National Academy of Sciences of the United States of America 105, 13764–13768.

Prado-Martinez, J., Sudmant, P.H., Kidd, J.M., et al., 2013. Great ape genetic diversity and population history. Nature 499, 471–475.

Prüfer, K., Munch, K., Hellmann, I., et al., 2012. The bonobo genome compared with the chimpanzee and human genomes. Nature 486, 527–531.

Prüfer, K., Racimo, F., Patterson, N., et al., 2014. The complete genome sequence of a Neanderthal from the Altai Mountains. Nature 505, 43–49.

Rak, Y., Ginsburg, A., Geffen, E., 2007. *Gorilla*-like anatomy on *Australopithecus afarensis* mandibles suggest *Au. afarensis* link to robust australopiths. Proceedings of the National Academy of Sciences of the United States of America 104, 6568–6572.

Rak, Y., 1983. The Australopithecine Face. Academic Press, New York.

Reich, D., Green, R.E., Kircher, M., et al., 2010. Genetic history of an archaic hominin group from Denisova Cave in Siberia. Nature 468, 1053–1060.

Reich, D., Patterson, N., Kircher, M., et al., 2011. Denisova admixture and the first modern human dispersals into Southeast Asia and Oceania. The American Journal of Human Genetics 89, 1–13.

Reno, P.L., Meindl, R.S., McCollum, M.A., et al., 2003. Sexual dimorphism in *Australopithecus afarensis* was similar to that of modern humans. Proceedings of the National Academy of Sciences of the United States of America 100, 9404–9409.

Richmond, B.G., Jungers, W.L., 2008. *Orrorin tugenensis* femoral morphology and the evolution of hominin bipedalism. Science 319, 1662–1665.

Rightmire, G.P., 1995. Geography, time and speciation in Pleistocene Homo. South African Journal of Science 91, 450–454.

Robinson, J.T., 1960. The affinities of the new Olduvai australopithecine. Nature 186, 456–458.

Robinson, J.T., 1961. The australopithecines and their bearing on the origin of man and of stone tool-making. South African Journal of Science 57, 3–13.

Rosas, A., Bastir, M., Martínez-Maza, C., et al., 2006. Inquiries into Neanderthal craniofacial development and evolution: "accretion" versus "organismic" models. In: Harvati, K., Harrison, T. (Eds.), Neanderthals Revisited: New Approaches and Perspectives. Springer, Dordrecht, pp. 37—70.

Rosenzweig, M.L., 1995. Species Diversity in Space and Time. Cambridge University Press, Cambridge.

Sawyer, S., Renaud, G., Viola, B., et al., 2015. Nuclear and mitochondrial DNA sequences from two Denisovan individuals. Proceedings of the National Academy of Sciences of the United States of America doi:10:1073/pnas.1519905112 (Early Edition).

Scally, A., Dutheil, J.Y., Hillier, L.W., et al., 2012. Insights into hominid evolution from the gorilla genome sequence. Nature 483, 169—175.

Schoetensack, O., 1908. Der Unterkiefer des *Homo heidelbergensis* aus den Sanden von Mauer bei Heidelberg. W. Engelmann, Leipzig.

Semaw, S., Simpson, S.W., Quade, J., et al., 2005. Early Pliocene hominids from Gona, Ethiopia. Nature 433, 301—305.

Senut, B., Pickford, M., Gommery, D., et al., 2001. First hominid from the Miocene (Lukeino Formation, Kenya). Comptes Rendus de l'Académie des Sciences 332, 137—144.

Senut, B., 1983. Les hominides Plio-Pleistocenes: essai taxinomique et phylogenetique a partis de certains os longs. Bulletins et mémoires de la Société d'Anthropologie de Paris 10, 325—334.

Shoshani, J., Groves, C.P., Simons, E.L., et al., 1996. Primate phylogeny: morphological vs. molecular results. Molecular Phylogenetics and Evolution 5, 101—153.

Slon, V., Sawyer, S., Renaud, G., et al., 2015. Proceedings of the European Society for the study of Human Evolution 207.

Smith, T.M., Tafforeau, P., Reid, D.J., et al., 2010. Dental evidence for ontogenetic differences between modern humans and Neanderthals. Proceedings of the National Academy of Sciences of the United States of America 107, 20923—20928.

Smith, R.J., 2005. Species recognition in paleoanthropology; implications of small sample sizes. In: Lieberman, D.E., Smith, R.J., Kelley, J. (Eds.), Interpreting the Past: Essays on Human, Primate, and Mammal Evolution in Honor of David Pilbeam. Brill Academic Publishers, Boston, pp. 207—219.

Spoor, F., Leakey, M.G., Gathogo, P.N., et al., 2007. Implications of new early *Homo* fossils from Ileret, east of Lake Turkana, Kenya. Nature 448, 688—691.

Spoor, F., Leakey, M.G., Leakey, L.N., 2010. Hominin diversity in the Middle Pliocene of eastern Africa: the maxilla of KNM-WT 40000. Philosophical Transactions of the Royal Society B 365, 3377—3388.

Spoor, F., Gunz, P., Neubauer, S., et al., 2015. Reconstructed *Homo habilis* type OH 7 suggests deep-rooted species diversity in early *Homo*. Nature 519, 83—86.

Stevens, N.J., Seiffert, E.R., O'Connor, P.M., et al., 2013. Palaeontological evidence for an Oligocene divergence between Old World monkeys and apes. Nature 497, 611—614.

Suwa, G., Asfaw, B., Beyene, Y., et al., 1997. The first skull of *Australopithecus boisei*. Nature 389, 489—492.

Suwa, G., Kono, R.T., Simpson, S.W., et al., 2009. Paleobiological implications of the *Ardipithecus ramidus* dentition. Science 326, 69—99.

Suwa, G., 1988. Evolution of the "robust" australopithecines in the Omo succession: evidence from mandibular premolar morphology. In: Grine, F.E. (Ed.), Evolutionary History of the "Robust" Australopithecines. Aldine de Gruyter, New York, pp. 199—222.

Tardieu, C., 1983. L'articulation du genou des Primates catarhiniens et Hominidés fossiles. Implications phylogénétique et taxinomique. Bulletins et Mémoires de la Société d'anthropologie de Paris 10 (Internet). Available from: http://www.persee.fr/web/revues/home/prescript/article/bmsap_0037-8984_1983_num_10_3_3908.

Tillier, A., 1982. Les enfants Néanderthaliens de Devil's Tower (Gibraltar). Zeitschrift für Morphologie und Anthropologie 73, 125—148.

Tobias, P.V., 1967. The Cranium and Maxillary Dentition of *Australopithecus (Zinjanthropus) boisei*. Cambridge University Press, Cambridge.

Tocheri, M.W., Orr, C.M., Larson, S.G., et al., 2007. The primitive wrist of *Homo floresiensis* and its implications for hominin evolution. Science 317, 1743—1745.

Uchida, A., 2004. Craniodental Variation Among the Great Apes. Harvard University Press, Cambridge.

Vannucci, R.C., Barron, T.F., Holloway, R.L., 2011. Craniometric ratios of microcephaly and LB1, *Homo floresiensis*, using MRI and endocasts. Proceedings of the National Academy of Sciences of the United States of America 108, 14043—14048.

Venn, O., Turner, I., Mathieson, I., et al., 2014. Strong male bias drives germline mutation in chimpanzees. Science 344, 1272—1275.

Villmoare, B., Kimbel, W.H., Seyoum, C., et al., 2015. Early *Homo* at 2.8 Ma from Ledi-Geraru, Afar, Ethiopia. Science 347, 1352—1355.

Von Koenigswald, G.H., Weidenreich, F., 1939. The relationship between *Pithecanthropus* and *Sinanthropus*. Nature 144, 926—929.

Ward, C.V., Kimbel, W.H., Harmon, E.H., et al., 2012. New postcranial fossils of *Australopithecus afarensis* from Hadar, Ethiopia (1990—2007). Journal of Human Evolution 63, 1—51.

Ward, C., Leakey, M., Walker, A., 1999. The new hominid species *Australopithecus anamensis*. Evolutionary Anthropology 7, 197—205.

Ward, C.V., Kimbel, W.H., Johanson, D.C., 2011. Complete fourth metatarsal and arches in the foot of *Australopithecus afarensis*. Science 331, 750—753.

Washburn, S.L., 1950. The analysis of primate evolution with particular reference to the origin of man. Cold Spring Harbor Symposia on Quantitative Biology 15, 67—78.

Weidenreich, F., 1940. Some problems dealing with ancient man. American Anthropologist 42, 375—383.

White, T.D., Johanson, D.C., Kimbel, W.H., 1981. *Australopithecus africanus*: its phyletic position reconsidered. South African Journal of Science 77, 445—470.

White, T.D., Suwa, G., Asfaw, B., 1994. *Australopithecus ramidus*, a new species of early hominid from Aramis, Ethiopia. Nature 371, 306—312.

White, T.D., Suwa, G., Asfaw, B., 1995. *Australopithecus ramidus*, a new species of early hominid from Aramis, Ethiopia — a corrigendum. Nature 375, 88.

White, T.D., WoldeGabriel, G., Asfaw, B., et al., 2006. Asa Issie, Aramis and the origin of *Australopithecus*. Science 440, 883—889.

White, T.D., Asfaw, B., Beyene, Y., et al., 2009. *Ardipithecus ramidus* and the Paleobiology of Early Hominids. Science 326, 64—86.

White, T., 2003. Early hominids — diversity or distortion? Science 299, 1994—1997.

Widianto, H., Zeitoun, V., 2003. Morphological description, biometry and phylogenetic position of the skull of Ngawi 1 (east Java, Indonesia). International Journal of Osteoarchaeology 13, 339—351.

Witmer, L.M., 1995. The extant phylogenetic bracket and the importance of reconstructing soft tissues in fossils. In: Thomason, J.J. (Ed.), Functional Morphology in Vertebrate Paleontology. Cambridge University Press, Cambridge, pp. 19–33.

Wolpoff, M.H., 1968. 'Telanthropus' and the single species hypothesis. American Anthropologist 70, 477–493.

Wolpoff, M.H., 1971. Competitive exclusion among lower Pleistocene hominids: the single species hypothesis. Man 6, 601–614.

Wood, B., 1984. The Origin of *Homo errectus*. Courier Forschungsinstitut Senckenberg, 69, 99–111.

Wood, B., Baker, J., 2011. Evolution in the genus *Homo*. Annual Review of Ecology, Evolution, and Systematics 42, 47–69.

Wood, B., Boyle, E.K., 2016. Hominin taxic diversity: fact or fantasy? American Journal of Physical Anthropology 159 (Suppl. 61), S37–S78.

Wood, B.A., Constantino, P., 2007. *Paranthropus boisei*: fifty years of evidence and analysis. Yearbook of Physical Anthropology 50, 106–132.

Wood, B., Harrison, T., 2011. The evolutionary context of the first hominins. Nature 470, 347–352.

Wood, B.A., Li, Y., Willoughby, C., 1991. Intraspecific variation and sexual dimorphism in cranial and dental variables among higher primates and their bearing on the hominid fossil record. Journal of Anatomy 174, 185–205.

Wood, B.A., 1974. Olduvai Bed I post-cranial fossils: a reassessment. Journal of Human Evolution 3, 373–378.

Wood, B.A., 1975. An Analysis of Sexual Dimorphism in Primates (Ph.D. thesis). The Unversity of London.

Wood, B.A., 1991. Koobi Fora Research Project, Volume 4: Hominid Cranial Remains. Clarendon Press, Oxford.

Wood, B.A., 1994. Taxonomy and evolutionary relationships of *Homo erectus*. In: 100 Years *Pithecanthropus Homo erectus* Problem, 171, pp. 159–165.

Wood, B.A., 2010. Systematics, taxonomy, and phylogenetics: ordering life, past and present. In: Larsen, C.S. (Ed.), A Companion to Biological Anthropology. Wiley-Blackwell, Oxford, pp. 56–73.

Woodward, A.S., 1921. A new cave man from Rhodesia, South Africa. Nature 108, 371–372.

Zipfel, B., DeSilva, J.M., Kidd, R.S., et al., 2011. The foot and ankle of *Australopithecus sediba*. Science 333, 1417–1420.

Zollikofer, C.P.E., Ponce de León, M.S., Lieberman, D.E., et al., 2005. Virtual cranial reconstruction of *Sahelanthropus tchadensis*. Nature 434, 755–759.

Chapter 3

The History of Early *Homo*

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For centuries humankind has sought the answer to what exactly makes us human: when did our history really begin?

Since 1776, when Linnaeus defined our genus as *Homo* (Linnaeus, 1735), scientists have identified several members of this genus, and in current encyclopedias of human evolution more than 50 members have been identified (Wood, 2011) and the number continues to rise (Berger et al., 2015). The debates intensify as the public becomes more interested in the issues of our human origins. Discoveries in this field frequently make the headlines as scientists announce the discovery of new *Homo* species. However, finding a balance between concrete evidence and theoretical claims has become a key task for all sciences, and particularly for paleoanthropology. The media is particularly interested in this field of sciences, which often causes premature claims of new species to be made.

There are several definitions for the human genus, but how can we sort out which is correct? It is simple enough to determine whether the definition is nonbiological or biological, and here we would not stop at Platonic notions or Biblical definitions of either man or species. When the theological and philosophical approaches are left aside, the scientific approach to human evolution clearly identifies stages in the development of this genus. Data that is based on theoretical biology, human fossils, and recent molecular studies all provide scientific insights into human evolution. This said, as human cultural beings, scientists will bring to the table discussions and methodological approaches that reflect known data, but also the foundations and presuppositions of their own knowledge, and with which they create models.

In the 19th century the dominant theory that the chimpanzee or gorilla was the ancestor of humans gradually became an obsession—to find the "missing link." This, in turn, created another misconception: that since man and ape are related, there must be a transitional fossil that could be found to prove it.

Today, scientists have reached a consensus that humans have much in common, anatomically and behaviorally, with other primates. This close biological relationship is supported by DNA evidence revealing that our closest living relatives are bonobos and chimpanzees. There is only about a one percent difference between the chimpanzee genome and our own, suggesting that we share a common ancestor. We thus have a relationship with the great apes that is more one of cousin-to-cousin than grandparent-to-grandchild, as was formerly believed.

The term "hominins" is now used to describe living humans and all other species from the lineage that diverged from that of chimpanzees around 7 Ma. Different hominins are represented by current and fossil records. The most ancient hominins became extinct without giving rise to new species. Although the relationships between different hominins are complex and often unresolved, aspects of their fossil remains have enabled us to place them, including *Homo*, into groups—or genera—to which our own species, *Homo sapiens*, belongs (Roberts, 2011; Potts and Sloan, 2010).

At the end of the 18th century, the German physiologist and anatomist, Johann Friedrich Blumenbach distinguished five races of the human species, and was one of the first scientists to study the identities of different species of primates (Blumenbach, 1969). In the 19th century, Charles Darwin stated that when the fossils of our ancestors were found, "light will be thrown on the origin of man and his history" (Darwin, 1871). His prediction has come true. Human fossils found in 1856 in the Neanderthal Valley (Germany) had strong eyebrows and a retreating forehead, which distinguished the species from modern man. In 1891, another important event in human evolutionary research brought to light the fossil Pithecanthropus in Java, which became known as *Homo erectus*.

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00003-X

A central turning point for the history of the genus *Homo* occurred in 1964 with the announcement by Louis Leakey, Phillip Tobias, and John Napier (Leakey et al., 1964). Their declaration from the Olduvai Gorge in Africa describing *Homo habilis* profoundly changed our understanding of human evolution. Several more landmark discoveries have provided new and critical information, yet many questions remain (Spoor, 2013; Spoor et al., 2015).

It is impossible to discuss the origin of the genus *Homo* without including "prehumans." Fossil evidence suggests that the first hominins appeared in Africa between 6 and 8 Ma, with many species appearing after this time. Their genetic relationships probably formed a complex web, some of which survived until relatively recently, and with several hominin species existing at the same time.

Specimens, such as *Sahelanthropus tchadensis* and *Orrorin tugenensis*, suggest that the earliest hominin species were modest in size, with brains no larger than those of modern apes, and exhibited a unique set of physical characteristics that allowed both upright walking and climbing.

The discovery in Chad of a 7 million year old hominin by Michel Brunet, is the oldest known to date. *S. tchadensis*, nicknamed "Tumai,u has revealed that this hominin already used semiterrestrial locomotion, judging by the time spent on the ground (Brunet et al., 2005; Brunet et al., 2002).

Over time, and in the context of changing selection pressures, populations appeared with new characteristics, and a number of evolutionary trends can be identified. Powerful jaws and large back teeth, ideal for chewing tough or fibrous foods, appear in some species. Brains that are large relative to body size, with smaller jaws and teeth, appear in others. Bipedalism became the dominant mode of locomotion, and all later hominins were characterized by their use of stone-tool technology.

The discovery of a 4.5 million year old *Ardipithecus* from Hadar, Ethiopia, brought new perspectives on how our earliest hominin ancestors—and our closest living relatives—evolved. The study of the *Ardipithecus* fossils, lead by Tim White, represents one of the best cases of detailed interdisciplinary study of early hominin specimens in the context of developmental biology, anatomy, ecology, biogeography, and geology (White et al., 2009).

Before finding *Ardipithecus*, fossils belonging to *Australopithecus* were regularly interpreted in a framework that used living African apes, especially chimpanzees, as proxies for the immediate ancestors of the human clade. Such projections were largely nullified by the discovery of *Ardipithecus* (White et al., 2015).

In today's scientific literature one can find different names for *Australopithecus* including *Australopithecus africanus*, *Australopithecus afarensis*, *Australopithecus aethiopicus*, *A. anamensis*, *Australopithecus garhi*, *Australopithecus bahrelghazali*, and *Australopithecus sediba*. *Australopithecus* can no longer be viewed as a short-lived transition between apes and humans. Instead, it represents an adaptive plateau occupied for ~3 million years by the lineages of four species of small-brained African bipeds (Roberts, 2011).

Although the half-million year interval between 2.5 and 3 Ma was a period of heightened morphological, taxonomic, and diet-driven adaptive diversity in extinct hominins, all of the known taxa from this interval are of *Australopith* grade. *Au. africanus* in South Africa, studied by R. Dart in 1924, showed that despite having small brains, early hominins could walk upright. The name "Australopithecus" means "southern ape" and was first given after the discovery of a remarkably preserved baby hominin skull known as the Taung Child.

While many specimens are fragmented or distorted, nearly all skeleton parts have been found in the *Au. africanus* fossils. Evidence points to a hominin whose growth and maturation were more similar to modern apes than to humans. Some adult skulls appear to have been much larger than others, which may indicate differences between the sexes and perhaps a harem-like social organization similar to that of modern gorillas. Alternatively, this variability in skull size may represent two different groups (Roberts, 2011; Potts and Sloan, 2010; Wood, 2011) (Fig. 3.1).

Australopithecus afarensis is one of the best-known early hominins, exemplified by the 3.2 million year old iconic skeleton known as "Lucy," found in 1974 in Hadar (Johanson), Ethiopia. The fragmented remains of several

FIGURE 3.1 "Skull 5", D4500, from Dmanisi, Georgia.

hundred *Au. afarensis* individuals have been discovered in East Africa, including males, females, and juveniles. Research has revealed evidence for both terrestrial and arboreal lifestyles, and extreme sexual dimorphism. The braincase is small compared to the body size, but the face and jaws are large. The thorax has an erect posture, and the shape of the legs suggests the species could walk upright, while other features, such as the length of the arms suggest good climbing ability. This group of fossils includes very large and very small individuals and there is debate as to whether this variation reflects the presence of two species, or one in which males and females have very different body size (Wood, 2011).

Hominins were widely distributed in Africa millions of years ago. *Australopithecus bahrelghazali* was found in Chad over 2500 km west of other hominin fossil sites in the Rift Valley (Brunet et al., 1995). Recent discoveries in South Africa of the *Au. sediba* species brought on more discussions around a possible "missing link" possessing a mixture of primitive (Australopith-like) and a derived (*Homo*-like) morphology (Berger et al., 2010). This was an attempt to promote *Au. sediba* as an ancestor of *Homo*, but it has not yet been accepted by the scientific community.

Indeed, it is impossible to present an overview of the entire history of research on our genus in this chapter. Symposia, review articles, exhibitions, etc. have been devoted to it at length, and syntheses are found in major scientific journals. The most recent reviews admit that there are many unresolved problems on the topic of our origins, and that although more fossils and archeological finds will continue to enhance our understanding of the evolution of early *Homo*, the comparative biology of mammals (including humans) will also continue to provide valuable frameworks for the interpretation of existing material. This comparative approach has been used to formulate and test robust models of the relationships between energy, life history, brain and body size, diet, mortality, and resource variability, and will yield a deeper understanding of human evolution (Schwartz and Tattersall, 2015; Aiello and Antón, 2012; Antón et al., 2014; Wood and Collard, 1999; Wood, 2014).

In my humble opinion, a main problem remains that of incomplete data. We now have great fossil discoveries, but very rarely do we find sites where we can integrate data on human anatomy (eg, both cranial and postcranial), clear stratigraphy and absolute age, or paleontological and archeological records.

THE FIRST *HOMO*

Homo habilis, considered the first member of the genus *Homo* that appears in fossil records, is associated with the earliest stone-tool technology. This species is characterized by a moderately large brain (Leakey et al., 1964) and exemplifies the lower end of the range of *Homo* fossil brain size (600 cm^3), with medium-sized molars and premolars compared to earlier hominins. It was a species that was usually relatively small in stature and more lightly built than most australopithecines but had a larger brain and a body capable of bipedal locomotion. The arms were longer and perhaps stronger than those of modern humans. However, there is enough variation in these traits across specimens to generate controversy. Some anthropologists have argued that these specimens should be placed within the genus *Australopithecus*, or that the taxon should be split into subgroups (Wood and Collard, 1999; Villmoare et al., 2015).

The type specimen (a specimen used to name and define a new species) of *H. habilis* consists of only one juvenile mandible. Other, more complete specimens are variably affiliated with *H. habilis*, but there is no consensus about their affiliations. Today scholars identify *Homo rudolfensis* by using only one specimen. Other candidates include an earlier specimen claimed by Villmoare et al. (2015), identified as a ~2.8 Ma mandible with some teeth (LD350-1) from Ethiopia's Ledi-Geraru, as being the earliest member of *Homo*. Another known fossil candidate is a 2.3 partial AL-666 (Kimbel et al., 1996; Berger et al., 2015), AL-666-1 (Hadar Formation, Ethiopia c. 2.3 Ma). This specimen, found in 2.3 million-year-old sediments at Hadar, Ethiopia, is a maxilla, most likely of a male individual, with most of the dentition (Kimbel et al., 1997).

Fossils differing from *Australopiths* appear in the Turkana Basin and in the Middle Awash region dating ca. 2.3 Ma, and it is very likely that *Homo* evolved in Africa. The earliest representatives of our genus are still poorly documented. Following the announcement of *H. habilis* in 1964, a number of specimens from Olduvai and other localities have been referred to this species. In addition, it has been argued that a second, larger-brained taxon is present in the record. Unfortunately, most of the remains are incomplete or damaged. It has proved especially difficult to define *H. rudolfensis*, as the proposed hypodigm includes only one intact cranium and nothing is known of the postcranial skeleton (Bromage et al., 1995). Whether one or two species should be recognized, and whether they are sufficiently like later humans to merit placement within *Homo*, are questions for which there is no clear consensus. Another early hominin found in this area includes the *Kenyanthropus platyops* (Leakey et al., 2012).

Most scientists consider that a major shift to humanlike patterns of cranial anatomy, body size, and behavior occurred with the emergence of *H. erectus* (eg, Antón, 2003; Shipman and Walker, 1989). Many researchers considered that *H. erectus* had numerous anatomical and life history hallmarks that are seen in modern humans. As the earliest nonerect *Homo* and *Australopithecus* were reconstructed as essentially bipedal apes, to some

researchers the gap between these groups suggested that earlier species, such as *H. habilis* should be excluded from *Homo* (Collard and Wood, 2007; Wood and Collard, 1999). The recent idea that habilis should belong to its own genus is also claimed (Wood, 2014).

THE DISCOVERY OF *HOMO ERECTUS*

Homo erectus was the first hominin species to be identified outside of Europe. With a type specimen from Java, Indonesia, it has been recognized from many sites across Asia, yet there is considerable disagreement as to whether European or African fossils should be included in this species. The Asian fossils, presented as the core fossil records of *H. erectus* from East and Southeast Asia, are dominated by skulls, jaws, and teeth. The few remains from other parts of the body are fragmented, show signs of disease, or are questionably dated, however taking these clues into account, it appears that *H. erectus* was a large-bodied, fully modern bipedal with a relatively large brain. The face and cranial vault were distinctive, with a strong brow region and wide cheekbones. Morphological variations in this species may be attributable to differences between the sexes, regional changes, or variations over time. The Javan *H. erectus* is remarkable for how long it lived there; evidence shows its presence as early as 1.8−1.7 Ma, and until only 25,000 years ago (Potts and Sloan, 2010).

China is also remarkable for its records of *H. erectus*. No fewer than 40 individuals were found at one site, the famous Zhoukoudian site near Beijing.

A large-brained skull of what was most likely an adult female *H. erectus* was discovered in Kenya. It was about 1.8 million years old, which shows that our own genus lived at the same time as other hominins. It is classified as *H. erectus*, but some scientists suggest that it, and other early African *H. erectus* fossils, should have their own species name, *Homo ergaster* (Kimbel et al., 2014; Kimbel, 2009; Wood, 2009).

The skulls and jawbones currently included in this species show a wide variation in shape and size. KNM-ER WT 15,000 is the most complete skeleton ascribed to *H. ergaster*, and in many respects (apart from the skull) it is very similar to modern humans: slender body frame and tall in stature, with relatively shorter arms and longer legs than any earlier hominin species. This change in limb and body proportions probably reflects the development of fully terrestrial bipedalism (Walker and Leakey, 1993).

H. erectus is usually thought to have originated in Africa before 1.80 MYA, therefore overlapping with *H. habilis* both temporally and geographically. However, recently some have questioned the species' African origins, suggesting that a more primitive form of *Homo* initiated the colonization of Eurasia.

Recently *Homo naledi* specimens have been discovered in South Africa. Opinions differ as to the phylogenetic (evolutionary) position of this species and its relevance to our understanding of the origins of the genus *Homo*, especially to the emergence of *H. erectus*. This incredibly rich collection of human fossils has been attributed by discoverers to previously unknown species of extinct hominin. *Homo naledi* is characterized by body mass and stature similar to small-bodied human populations, but with a small endocranial volume (around 400 c3) similar to *Australopiths.* The cranial morphology of *H. naledi* is unique, but similar to early *Homo* species including *H. erectus*, *H. habilis*, and *H. rudolfensis*. Although primitive, the dentition is generally small and simple in occlusal morphology. *H. naledi* has humanlike manipulatory adaptations of the hand and wrist and a humanlike foot and lower limb. These humanlike aspects contrast in the postcrania with more primitive or *Australopith*-like features (Berger et al., 2015). Scientists who oppose accepting *H. naledi* as a new species stress that the same characteristics are found in other *Homo* species, particularly *H. erectus*. Main problems remain a lack of clear dating and the ambiguous geological contexts of the site.

DMANISI

As a case for the early *Homo*, I would like to present the story of hominins from Dmanisi, Georgia, in more detail. Since I have been working at the site since 1991, I believe that in Dmanisi we have very complete evidence about anatomy, paleoenvironment, way of life, and behavior of early *Homo* (Fig. 3.2).

For a long time, scientists thought that the first hominin out-of-Africa migrants were those with large brains and a stature approaching human dimensions. This group was widely assumed to have stepped out of Africa into the world around 1 Ma, once their greater intelligence, more modern and humanlike body proportions had evolved, and once they had invented more advanced stone tools.

Georgia, in the Caucasus, is known as the country of the Golden Fleece and of the earliest wine culture. The wealth of prehistoric finds from Dmanisi has put it on the scientific map in terms of the earliest Paleolithic period. Dmanisi is in Southern Georgia about 85 km from the capital Tbilisi, and was a medieval city situated on a hilltop. In 1983, archeological excavations in the ruins of the old city led to the fortuitous discovery of Plio-Pleistocene sediments containing animal bones. Following this, stone tools and hominin remains were recovered from the site (Fig. 3.3).

The archeological site is on a promontory overlooking the confluence of the Pinazauri and Mashavera Rivers. These rivers eroded through 80−100 m of basalt beginning in the early Pleistocene, leaving the site high above the rivers today. Scientists dated the age of the fossils using

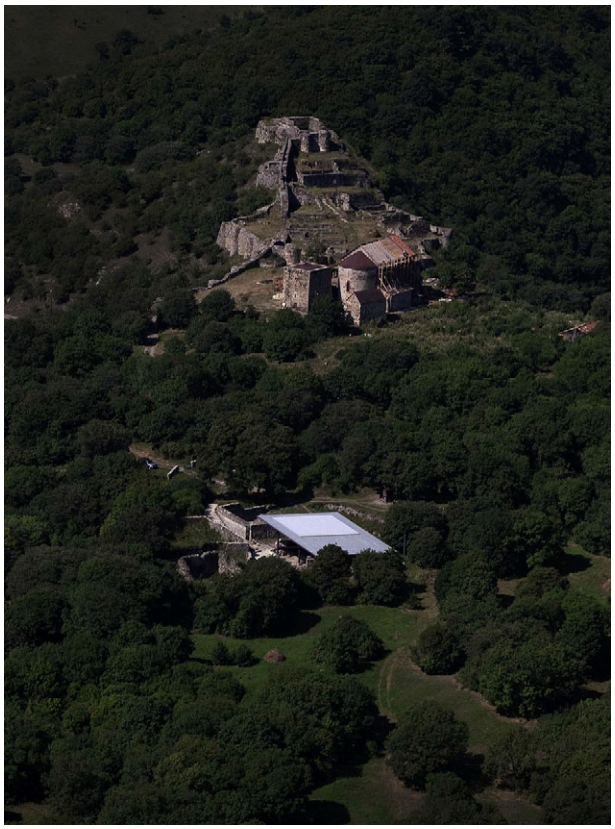

FIGURE 3.2 Aerial photo of Dmanisi Archaeological Museum-Reserve.

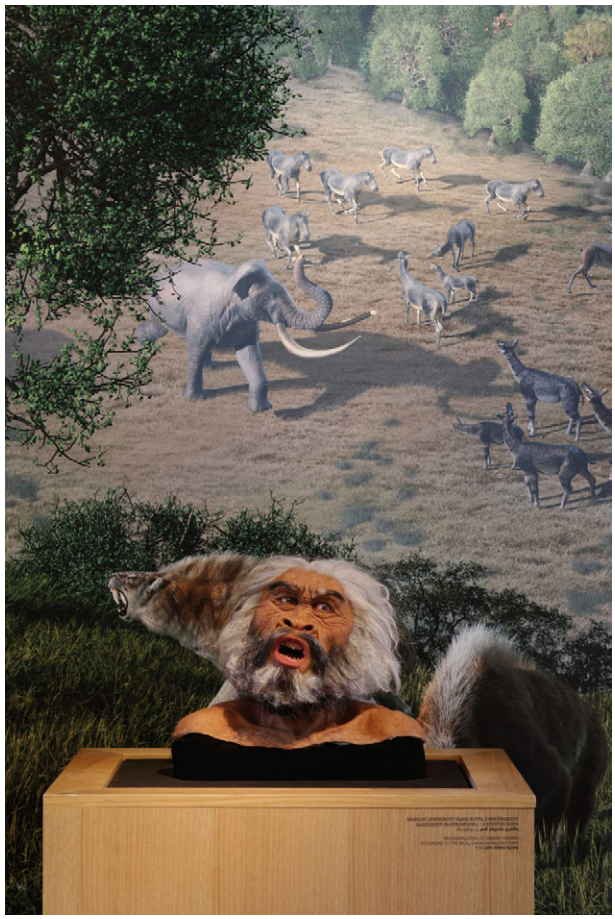

FIGURE 3.3 Reconstruction of the "Skull 5" from Dmanisi by Paleo-Artist John Gurche.

radiometric techniques from deposits directly atop a thick layer of volcanic rock dating from 1.85 Ma. The fresh, unweathered contours of the basalt indicate that little time had passed before the fossil-bearing sediments blanketed it. Paleomagnetic analyses show that sedimentation occurred around 1.77 Ma, when Earth's magnetic polarity reversed, a phenomenon called the "Matuyama Reversal" (Gabunia et al., 2000).

Remains of known prehistoric animals accompany the hominin fossils found here—a rodent called *Mimomys*, for instance, only lived between 1.6 and 2.0 Ma. The 1.76 million year old layer of basalt at a nearby site caps the same stratigraphy. Dmanisi is a snapshot of time, like a time capsule (Fig. 3.4).

HOMININS

The Dmanisi site has offered up the remains of several hominin individuals (5 skulls—4 with maxillas; 4 mandibles; and 100 postcranial remains). This is the richest and most complete collection of indisputable early *Homo* remains from any single site with a comparable stratigraphic context. The Dmanisi sample comprises variations according to age: subadult D2700/D2735 with erupting M3s. The cast of this skull and mandible can be seen in the exhibit; adults D2280, D2282/D211, D4500/D2600; old individuals D3444/D3900 and sexual dimorphism. Despite certain anatomical differences between the Dmanisi specimens, we do not presently see sufficient grounds to assign them to more than one hominin taxon. Thus, the Dmanisi assemblage offers a unique opportunity to study variability within an early *Homo* population.

Our analyses show that the Dmanisi people were small (c. 150 cm). Related to body size, their brains were smaller (545−760 cm^3) than those of "classic" *H. erectus* from Africa and Asia (800−1000 cm^3) (Lordkipanidze et al., 2007; Rightmire and Lordkipanidze, 2009). In this respect, they are closer to the very first representatives of the genus *Homo* (*H. habilis* from Africa, c. 2 Ma) than to their later conspecifics. Dmanisi people were almost modern in their body proportions, and were highly efficient walkers and runners, but their brains were tiny compared to ours, and their arms moved in a different way.

The Skull 5 cranium with its mandible, found earlier, represents the world's first completely preserved adult hominin skull from the early Pleistocene. It has the smallest braincase of the Dmanisi individuals (546 cm^3, or about one-third that of a modern human), but the largest

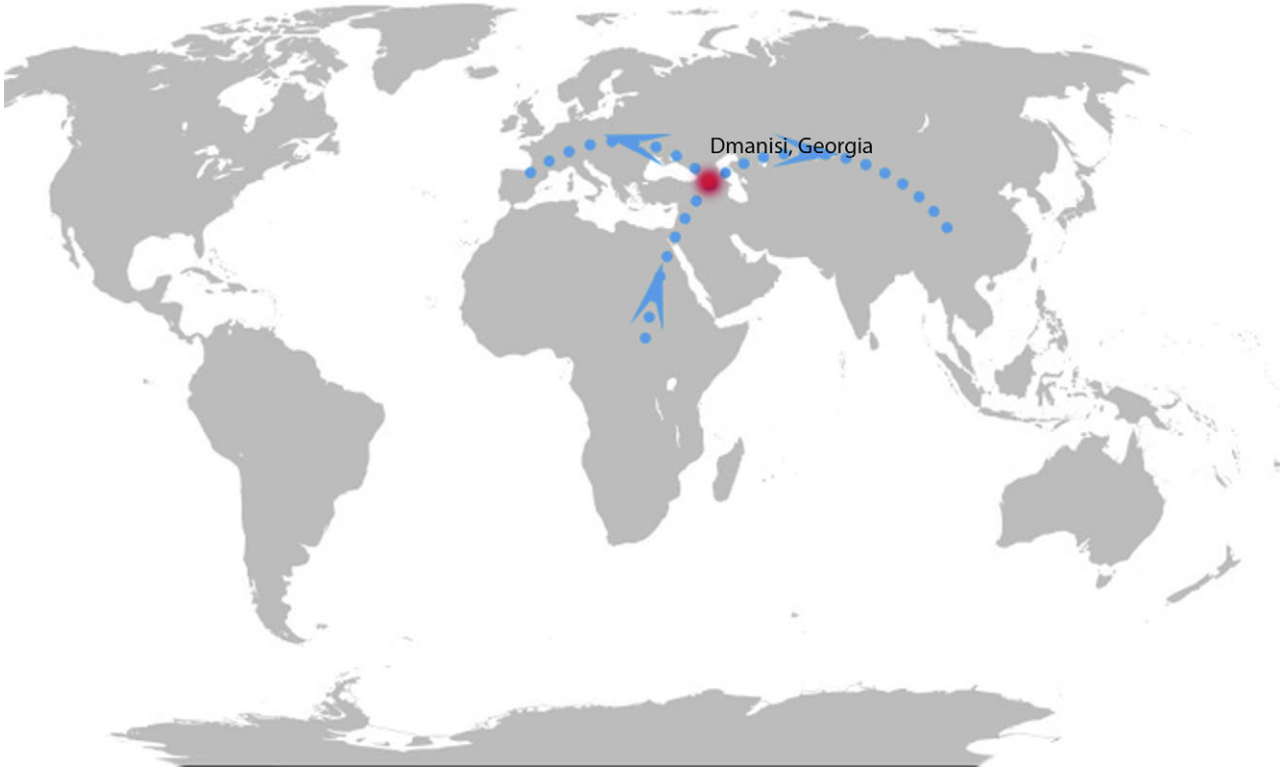

FIGURE 3.4 Possible migration roots of early *homo*.

face and teeth—a combination previously unknown for early *Homo*. The skull's face, large teeth, and small brain size resemble those of earlier fossil humans, but the detailed anatomy of its braincase, which gives clues to the "wiring" of the brain, is similar to that of the more recent early human species, *H. erectus*. The Dmanisi site has fueled an ongoing discussion over whether the Dmanisi humans were an early form of *H. erectus*, a distinct species called *Homo georgicus*, or something else (Fig. 3.5).

PALEOENVIRONMENT

Faunal and paleobotanical evidence makes it possible to reconstruct the ecology of the Dmanisi hominins. At the time of occupation, the site was near a lake shore that formed when the Masavera lava flow dammed the Masavera and Pinasaouri Rivers. At the Dmanisi site more than 50 groups of animals have been identified; faunal remains include several large carnivores, bovids, an equid, and other

FIGURE 3.5 Dmanisi Hominins, from left to right D4500 cranium, 2600 mandible, 211 mandible and D2700 cranium.

open-steppe and gallery-forest taxa. In Dmanisi we found bones of saber-tooth cats, giraffes, rhinos, elephants, and other extinct animals. The data reflect a paleoenvironment that spread like a mosaic over a large area around the site: woodland and gallery forests, bush land, tree savannahs, open grasslands, and semidesert-like rocky terrains with shrub vegetation. Generally, Dmanisi was a forested, relatively humid habitat in a temperate zone, with cool winters. In contrast, East Africa had a relatively dry and hot steppic environment.

STONE TOOLS

The Dmanisi site is very rich archeologically, where more than 10,000 stone tools have been discovered. The site preserves a complex archeological record of numerous reoccupations, measured by both stratigraphic and spatial concentrations of artifacts and faunal remains across all areas of the site.

While flakes comprise the majority of tools recovered, some cores and choppers have also been found. The raw materials for lithic artifacts come from nearby rivers. The differences in technology are not only observed in the changes in the material composition of the assemblages, but also the techniques. Before the Dmanisi finds, experts believed that humans could not have left Africa before having developed an advanced technology, such as Acheulean types of tools that were symmetrically shaped, manufactured, and standardized. The tools found at Dmanisi, however, are simple flakes and choppers, much the same as the primitive Oldowan tradition that hominins in Africa practiced nearly a million years earlier.

We found many unmodified stones at the site originating from elsewhere; there was no possible way they could have arrived there naturally. The larger rocks were likely used as tools for pounding flesh, cutting meat, or smashing bones, while certain smaller stones might have served different purposes, such as enabling aggressive scavenging. Small hominins who lived there stuck together for protection and perhaps threw rocks to pilfer food from carnivores (Ferring et al., 2011).

Evidence including lithics and fossil human anatomy supports the hypothesis that the initial evolution of "elite human throwing" arose as part of power-scavenging and/or hunting adaptation. The capacity to throw with elite skill is expected to have had important social consequences and to have driven the evolution of a uniquely human type of kinship-dependent social cooperation. The evolution of elite throwing for power-scavenging is a catalytic "accident" or "preadaptation" that set off a social revolution producing a uniquely human species (Bingham and Souza, 2011).

Other indirect evidence of social cooperation comes from the human skull D-3444 cranium and jaw. These fossils belonged to an individual who had lost all but one of his teeth before he died. How could a toothless person survive for years in a cold environment, without using fire to cook food? The consumption of soft animal tissues, such as marrow and brains is indicated by associated mammal bones and pounding tools. Even more compelling is the possibility that he was cared for (Lordkipanidze et al., 2005).

POST–*HOMO ERECTUS* EVIDENCE

No complete skeletons have been found for *Homo antecessor*, but some parts of the body, including the skull, thorax, and feet, are well represented in the disarticulated and mixed fossil collection from Gran Dolina, Spain (Carbonel et al.). Together, these fossils suggest that the *H. antecessor* population was of a similar average stature to modern humans and fully bipedal, but with longer, more slender arms and wider chests. The skull of the species was rounded and quite lightly built, with an average brain capacity of approximately 1000 cc. This species' face would have had a remarkably modern appearance, including a prominent nose, but receding chin.

Many skulls from Europe and Africa are ascribed to *Homo heidelbergensis*, but much of what is known about the rest of the body comes from the Sima de los Huesos fossil collection. This includes the remains of at least 30 individuals, mostly young adult men, women, and juveniles. Bone analyses have shown that *H. heidelbergensis* was robust and relatively tall, with adult males averaging 1.75 m (5 ft, 9 in.). Some skeletons show evidence of disease and healed injuries, perhaps reflecting the harsh conditions of Pleistocene Europe.

The path to our modern physical form is anything but clear, yet there are many fossil clues and theories about how it happened. One of the most controversial issues is whether *H. sapiens*—our species—evolved and eventually replaced all other hominins, or whether there was instead a global blending of genes that led to our species evolving everywhere more or less at the same time.

Key players in this process were *H. heidelbergensis* and an archaic *H. sapiens*. Some scientists view these two as species that evolved later in two different directions: *H. heidelbergensis* led to Neandertals (*Homo neanderthalensis*); and archaic *H. sapiens*, at least the African form also known as *Homo rhodesiensis*, led to *H. sapiens*. The oldest human DNA comes from 300,000 to 400,000 year old human bones classified as *H. heidelbergensis* found in Spain's Sima de los Huesos site.

Genetic studies and new African fossil finds, such as *Homo sapiens idaltu*, a hominin that has both archaic and anatomically modern *H. sapiens* features, suggest that Neandertals and modern humans went their separate ways genetically about 600,000 years ago. Many scientists see this evidence as strong support for the view that *H. sapiens* evolved in Africa and then completely replaced the Neandertals and any other hominins living at the same time. This view, however, is still debated.

HOBBIT

Scholars were stunned a decade ago to learn that *H. erectus* might have survived on the island of Java in Indonesia until 25,000 years ago, well after the arrival of *H. sapiens* in the region and even after the disappearance of Europe's Neandertals.

The recent revelation that a third hominin, dubbed *Homo floresiensis*, also lived in the area until just 12,000 years ago has proven even more provocative. Archeologists recovered the remains of *H. floresiensis* from a large limestone cave known as Liang Bua located in western Flores. *H. floresiensis*, nicknamed "Hobbit," has been estimated to have a height of about 1−1.10 m, and a body weight of 25 kg, with a remarkably small brain of less than 400 cm^3. The critics of establishing the new species argue that peculiarities are a result of diseases, particularly microcephaly, and that *H. floresiensis* is a small *H. sapiens*.

No one knows exactly how humans first reached the island of Java—they may have made the sea crossings by boat, or may have drifted from natural rafts by accident. For me, the most logical explanation is that we have a case of insular dwarfism previously unknown in humans.

Geographically, the Javan *H. erectus* is a good candidate for being the ancestor of *H. floresiensis*; however, its resemblance to specimens from Africa and from Dmanisi raise the question of whether *H. floresiensis* stemmed from a different hominin migration into Southeast Asia than the one that evolved into the Javan *H. erectus.* Future excavations on Flores and other Indonesian islands may cast light on these mysteries.

CONCLUSION: WHAT WE LEARNED FROM THE DMANISI CASE

The main components distinguishing *Homo* and more primitive hominins are brain and body size, posture, locomotion, and of course culture. Tool manufacture is considered under culture, and there are several claims of tool use in non-*Homo* hominins, claims fueled by the discovery of 3.3 million-year-old tools (Harmand et al., 2015). The brain size of 600 cm for *Homo* was a long-standing distinguishing element; however the Naledi, Flores, and Dmanisi fossils invalidate this.

The Question: Is *Homo habilis* the First *Homo*?

Considering its brain and body proportions, the characteristics of its jaws and teeth, and features related to locomotion, *H. habilis* is more Australopith-like than previously thought. The emergence of *H. erectus* (without distinguishing either *H. ergaster* or *H. georgicus*) could be considered as the birth of our genus. I think it's premature to classify *H. naledi*, however. I am sure that soon we will learn the age of these fantastic fossils, and then will be able to place them in the evolutionary tree.

So if *H. erectus* is indeed the first representative of our genus, the best hard evidence we have comes from Dmanisi. We have never had such accurately dated material, so many well-preserved human fossils—both cranial and postcranial—or such a rich fauna and thousands of stone tools from any other single site.

Here we discovered Skull 5, the world's first completely preserved adult hominin skull from the early Pleistocene. It has a small braincase of 546 cm^3 (about one-third of a modern human's), but the largest face and teeth, a combination previously unknown for early *Homo*. Dmanisi has indeed yielded multiple fossils of the same geological age and from a single locality. This provides the first opportunity to actually quantify and test hypotheses about intra- and interspecific variation in early *Homo*. Skull 5 is key to these analyses because it unites features that have been used to define different species of early *Homo*. In other words, had the braincase and the face of Skull 5 been found as separate fossils in Africa, they might have been attributed to different species (Fig. 3.6).

Comparing variations in the Dmanisi sample with variations in modern human and chimpanzee populations now shows that all the Dmanisi individuals belong to a population of a single early *Homo* species. Indeed, the five Dmanisi individuals are conspicuously different from each other, but not more different than any five modern human individuals, or five chimpanzee individuals from a given population. Dmanisi has let us capture a clear snapshot of the evolution of early *Homo*.

What is the most complete portrait of representative of the genus *Homo*? As we mentioned already Dmanisi draws the most complete picture.

We have a group of creatures with small brains, small stature, with very developed lower limbs, and highly

FIGURE 3.6 Reconstruction of Dmanisi hominins by Paleo-Artist Elisabeth Daynes.

efficient walkers and runners with almost modern body proportions; and though their arms moved in a different way, they use primitive stone tools and have a social system; also, they live in a temperate environment, very different from Africa.

Yet, in spite of these exciting discoveries, the early evolution of the genus *Homo* and the number of species is still shrouded in mystery. The hypothesis that early *Homo* represents one variable species versus multiple species is still in progress (Spoor, 2013). We are not rejecting the possibility of a number of *Homo* species, but I do not think this issue should be considered a simple discussion between "splitters" and "lumpers." Indeed, the senior authors of our article on Skull 5 (See Lordkipanidze et al., 2013 and Zollikofer et al., 2014), which is considered an additional "lumping" paper, were among the first to show—through quantitative data—that Neandertals and modern humans are two separate species.

The extraordinary preservation of Dmanisi specimens from different biological ages has enabled us to use approaches from population biology. Thus, the Dmanisi finds have brought new standards to these discussions. I am sure that the discovery of new fossils and the further development of scientific methods will shed more light on why and how both of these seemingly divergent approaches to taxonomy—and perhaps uniquely new paradigms—will contribute to understanding the history of our species.

ACKNOWLEDGMENT

This publication was prepared in the framework of the Humboldt Research Award.

REFERENCES

Aiello, L.C., Antón, S.C., 2012. Human biology and the origins of *Homo*: an introduction to Supplement 6. Current Anthropology 53 (Suppl. 6), S269–S277. http://dx.doi.org/10.1016/B978-0-12-420190-3.00003-X.

Antón, S., 2003. A natural history of Homo erectus. Yearbook of Physical Anthropology 46, 126–170.

Antón, S., Potts, R., Aiello, L., 2014. Evolution of early *Homo*: an integrated biological perspective. Science 345 (6192).

Berger, L.R., de Ruiter, D.J., Churchill, S.E., et al., 2010. *Australopithecus sediba*: a new species of *Homo*-like Australopith from South Africa. Science 328 (5975), 195–204.

Berger, C., Lee, R., Hawks, J., Ruiter, D., et al., 2015. A new hominin from the Upper Miocene of Chad, *Homo naledi*, a new species of the genus *Homo* from the Dinaledi Chamber, South Africa. eLife 4. http://dx.doi.org/10.1016/B978-0-12-420190-3.00003-X.

Bingham, P.M., Souza, J., 2011. Death from a Distance and the Bird of the Humane Universe: Human Evolution, History and Your Future, Kindle ed. BookSurge, South Carolina.

Blumenbach, J.F., 1969. On the Natural Varieties of Mankind (De Generis Humani Varietate Nativa). Bergman, New York, vol. 1775 and 1795 treatises.

Bromage, T.G., Schrenk, F., Zonneveld, F.W., 1995. Paleoanthropology of the Malawi Rift. An early hominin mandible from the Chiwondo Beds, northern Malawi. Journal of Human Evolution 28, 71–108. http://dx.doi.org/10.1016/B978-0-12-420190-3.00003-X.

Brunet, M., Beauvilain, A., Coppens, Y., et al., 1995. The first australopithecine recovered west of the Rift Valley (Koro Toro region, Republic of Chad). Nature 378, 273–275.

Brunet, M., Guy, F., Pilbeam, D., et al., 2002. A new hominin from the Upper Miocene of Chad, central Africa. Nature 418, 145–151.

Brunet, M., Guy, F., Pilbeam, D., et al., 2005. New material of the earliest hominin from the Upper Miocene of Chad. Nature 434, 753–755.

Collard, M., Wood, B., 2007. Hominin homoiology: an assessment of the impact of phenotypic plasticity on phylogenetic analyses of humans and their fossil relatives. Journal of Human Evolution 52 (5), 573–584.

Darwin, C., 1871. The Descent of Man. John Murray, London.

Ferring, R., Oms, O., Agust, J., et al., 2011. Earliest human occupations at Dmanisi (georgian Caucasus) dated to 1.85–1.78 Ma. Proceedings of the National Academy of Sciences of the United States of America 108, 10432–10436.

Gabunia, L., Vekua, A., Lordkipanidze, D., et al., 2000. Early Pleistocene hominin cranial remains from Dmanisi, Republic of Georgia: taxonomy, Geological Setting and age. Science 288, 1019–1025.

Harmand, S., Lewis, J.E., Feibel, C.S., et al., 2015. 3.3-million-year-old stone tools from Lomekwi 3, west Turkana, Kenya. Nature 521, 310–315.

Kimbel, W.H., et al., 1996. Late Pliocene *Homo* and Oldowan tools from the Hadar Formation (Kada hadar member), Ethiopia. Journal of Human Evolution 31, 549–561. http://dx.doi.org/10.1016/B978-0-12-420190-3.00003-X.

Kimbel, W.H., Johanson, D.C., Rak, Y., 1997. Systematic assessment to maxilla of Homo from Hadar, Ethiopia. American Journal of Physical Anthropology 103, 235–262.

Kimbel, W.H., Suwa, G., Asfaw, B., et al., 2014. *Ardipithecus ramidus* and the evolution of the human cranial base. Proceedings of the National Academy of Sciences of the United States of America 111 (3), 948–953.

Kimbel, W.H., 2009. In: Grine, F.E., Fleagle, J.G., Leakey, R.E. (Eds.), The First Humans: Origin and Early Evolution of the Genus Homo, Vertebrate Paleontology and Paleoanthropology Series. Springer, Dordrecht, Netherlands, pp. 31–38.

Leakey, L.S.B., Tobias, P.V., Napier, J.R., 1964. A new species of the genus *Homo* from Olduvai Gorge. Nature 202, 7–9.

Leakey, M.G., et al., 2012. New fossils from Koobi Fora, northern Kenya, confirm taxonomic diversity in early *Homo*. Nature 488, 201–204.

Linnaeus, C., 1735. System a Natura Eperregnatrianaturae, Secundum Classes, Ordines, Genera, Species Cum Char – Acteribus, Differentiis, Synonymis, Locis. Laurentii Salvii, Stockholm.

Lordkipanidze, D., Vekua, A., Rightmire, G.P., et al., 2005. The first edentulous hominin skull. Nature 434, 717–718.

Lordkipanidze, D., Jashashvili, T., Vekua, A., et al., 2007. Postcranial evidence from early *Homo* from Dmanisi, Georgia. Nature 449, 305–310.

Lordkipanidze, D., Ponce de León, M.S., Margvelashvili, A., et al., 2013. Complete skull from Dmanisi, Georgia, reveals evolutionary biology of early *Homo*. Science 342, 326–331.

Potts, R., Sloan, C., 2010. What Does it Mean to Be Human? National Geographic, ISBN 978-1-4262-0606-1.

Rightmire, G.P., Lordkipanidze, D., 2009. In: Grine, F.E., Fleagle, J.G., Leakey, R.E. (Eds.), The First Humans: Origin and Early Evolution of the Genus Homo, Vertebrate Paleontology and Paleoanthropology Series. Springer, Dordrecht, Netherlands, pp. 39–48.

Roberts, A., 2011. In: Guerrero, A.G. (Ed.), Evolution, the Human Story. ISBN:978-1-4053-6165-1.

Shipman, P., Walker, A., 1989. The costs of being a predator. Journal of Human Evolution 18, 373–392.

Schwartz, J.H., Tattersall, I., 2015. Defining the genus *Homo*. Science 349 (6251), 931–932.

Spoor, F., Gunz, P., Neubauer, S., et al., 2015. Reconstructed *Homo habilis* type OH 7 suggests deep-rooted species diversity in early *Homo*. Nature 83–86.

Spoor, F., 2013. Palaeoanthropology: small-brained and big-mouthed. Nature 502, 452–453. http://dx.doi.org/10.1016/B978-0-12-420190-3.00003-X. PMID: 24153292.

Villmoare, B., Kimbel, V., Seyoum, C., 2015. Early *Homo* at 2.8 Ma from Ledi-Geraru, Afar, Ethiopia. Science 347 (6228), 1352–1355.

Walker, A., Leakey, R. (Eds.), 1993. The Nariokotome Homo Erectus Skeleton. Harvard Univ. Press, Cambridge, MA.

White, T.D., et al., 2009. *Ardipithecus ramidus* and the paleobiology of early hominins. Science 326 (5949), 75–86.

White, T., Lovejoy, O., Asfaw, B., et al., 2015. Neither chimpanzee nor human, *Ardipithecus* reveals the surprising ancestry of both. PNAS 112 (16), 4877–4884.

Wood, B., Collard, M., 1999. The human genus. Science 284, 65–71. http://dx.doi.org/10.1016/B978-0-12-420190-3.00003-X. PMID: 10102822.

Wood, B., 2009. In: Grine, F.E., Fleagle, J.G., Leakey, R.E. (Eds.), The First Humans: Origin and Early Evolution of the Genus Homo, Vertebrate Paleontology and Paleoanthropology Series. Springer, Dordrecht, Netherlands.

Wood, B. (Ed.), 2011. Wiley-Blackwell Encyclopedia of Human Evolution. Wiley-Blackwell. ISBN 978-1-4051-5510-6.

Wood, B., 2014. Fifty years after Homo habilis. Nature 508, 31–33.

Zollikofer, C., Ponce de Leon, M.S., Margvelashvili, A., et al., 2014. Response to comment on "a complete skull from Dmanisi, Georgia, and the evolutionary biology of early *Homo*". Science 344–360.

Chapter 4

The Contribution of Genetic Ancestry From Archaic Humans to Modern Humans

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MODELS OF HUMAN ORIGINS

For many years, many anthropologists, archaeologists, geneticists, and other researchers were kept busy trying to answer the following question: what were the circumstances leading to the origins of our own species, anatomically modern humans (hereafter referred to as AMH)? Although there were various models proposed over the years, beginning in the 1980s three models dominated this discussion, as reviewed in more detail elsewhere (Stoneking, 2008): a recent African origin (RAO) with complete replacement of non-African archaic humans; an RAO with assimilation of non-African archaic humans; and multiregional evolution. All three models (Fig. 4.1) take as their starting point the paleontological evidence that indicates that archaic species of *Homo* began migrating out of Africa around 1.8–2.0 Ma, and spread throughout the Old World, evolving into various different groups of archaic humans. According to both RAO models, modern humans subsequently arose in Africa more recently, around 250 Ka, and began dispersing from Africa to the rest of the world beginning around 60–90 Ka. The two RAO models then differ in terms of what happened next: according to the RAO with replacement (RAO-R) model, AMH completely replaced all non-African archaic humans with no interbreeding; according to the RAO with assimilation (RAO-A) model, AMH interbred with some archaic humans. There are different versions of the RAO-A model, positing different amounts of interbreeding between archaic humans and AMH in different parts of the world. For example, one version suggests that interbreeding occurred only between Neandertals and AMH, while another version suggests that interbreeding occurred between AMH and archaic humans in Australasia but nowhere else. The crucial distinction between the RAO-R model and these various RAO-A models is that the RAO-R model predicts that there is no non-African archaic human ancestry in AMH, whereas the RAO-A models predict that there is some archaic human ancestry in AMH in some parts of the world.

In contrast to the various RAO models, which posit a single distinct origin of AMH in Africa and then spread throughout the Old World, multiregional evolution instead holds that there was no single distinct origin of AMH anywhere in the world (Wolpoff et al., 1984). Instead, following the initial dispersal of *Homo* from Africa some 1.8–2.0 Ma, the entire Old World population of archaic humans (encompassing Africa, Europe, Asia, and Australasia) evolved in concert, via gene flow between populations as well as regional developments due to selection, to become modern humans, without any major exodus from Africa (or any other region in the world).

Thus, according to the RAO model, all modern human populations should show a genetic signature of highest genetic diversity in Africa (since this is the source of all modern populations); diversity outside of Africa should be a subset of that within Africa; and human populations should be closely related, having diverged only in the past 60–90 Ka. By contrast, the multiregional evolution model predicts that there should be no indication of a single source of genetic diversity in modern populations, as all Old World populations of archaic hominins contributed to the genetic diversity of modern populations, and moreover the genetic divergence among human populations should be quite old, as much as 1.5–2 Ma.

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00004-1

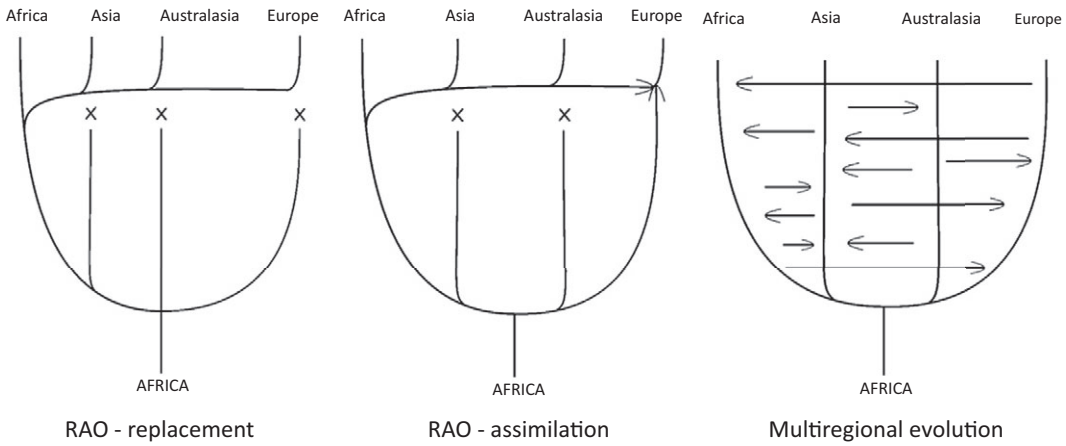

FIGURE 4.1 Models for the origins of modern humans. *Adapted, with permission, from Stoneking, M., 2008. Human origins. The molecular perspective. EMBO Report 9 (Suppl. 1), S46–S50.*

Although all of these models were originally proposed based on fossil and archaeological evidence (Stringer and Andrews, 1988; Wolpoff et al., 1984), distinguishing among them based on such evidence proved very difficult. The resolution of the at times contentious debate over these models was ultimately provided by genetic evidence, first from contemporary humans, and then more recently with the addition of genomic data from archaic humans. A simple prediction of the RAO models is that human populations should show a genetic signature of highest genetic diversity in Africa (since this is the source of all modern populations), and moreover the genetic diversity outside of Africa should be a subset of that within Africa. In addition, all human populations should be relatively closely related, having diverged only in the past 60–90 Ka. By contrast, the multiregional evolution model predicts that there should be no strong indication of a single source of genetic diversity in modern populations, as all Old World populations of archaic hominins contributed more or less equally to the genetic diversity of modern populations, and moreover the genetic divergence among human populations should be quite old, as much as 1.8–2.0 Ma. Thus, these different models make contrasting predictions that can be tested with genetic evidence.

The first genetic evidence to bear on this issue came from mitochondrial DNA (mtDNA), a small, circular genome found in the mitochondria (structures that produce energy) of cells. MtDNA has the convenient property of being strictly maternally inherited, so it reflects the maternal history of human populations (Pakendorf and Stoneking, 2005). Beginning in the late 1980s, a series of studies convincingly and consistently showed that the roots of human mtDNA diversity were in Africa, that the mtDNA variation outside of Africa is a subset of that in Africa, and that human mtDNA variation arose within the past 150–250 Ka (Cann et al., 1987; Ingman et al., 2000; Vigilant et al., 1991). Thus, human mtDNA variation appears to support the RAO models.

Analyses of variation in the Y-chromosome (which is the male counterpart to mtDNA, as the Y-chromosome is passed on from fathers to sons and hence reflects the paternal history of human populations) came to similar conclusions, namely greatest diversity within Africa; variation outside Africa is a subset of that within Africa; and human Y-chromosome variation has a recent origin (Underhill et al., 2000). Analyses of dense genome-wide datasets (consisting of thousands to millions of genetic markers distributed all across the genome, and more recently, whole genome sequences) have come to similar conclusions (1000 Genomes Consortium, 2012; Li et al., 2008; Prugnolle et al., 2005; Rosenberg et al., 2002). In sum, there is a strong and consistent signature of an RAO all across our genome, which supports the RAO model and refutes the multiregional evolution model (Stoneking, 2008).

However, distinguishing between RAO-R versus RAO-A proved more difficult with genetic data only from contemporary populations. Several studies attempted to address this question by looking for unusual patterns of genetic variation that could not be accounted for by the RAO-R model. For example, genes that show deeper divergences among non-African populations than between African and non-African populations could be the signature of interbreeding between modern humans and non-African archaic hominins (Wall and Hammer, 2006), and some studies claimed to find such evidence (Garrigan et al., 2005; Harding et al., 1997; Harris and Hey, 1999). However, the results were equivocal, as it is extremely difficult to rule out that such unusual patterns are not simply due to inadequate sampling of African genetic diversity, the influence of natural selection, or even just chance (Fagundes et al., 2007).

The advent of new methods for obtaining and sequencing DNA from ancient remains (reviewed in Stoneking and Krause, 2011) provided an opportunity to address the question of admixture by directly screening AMH genomes for segments of DNA that might have come from archaic humans. Indeed, the first such ancient DNA analysis, of mtDNA from the Neandertal type specimen (Krings et al., 1997), found that Neandertal mtDNA falls outside the range of modern human mtDNA variation. All subsequent studies of Neandertal mtDNA have confirmed the original observation (Briggs et al., 2009); thus there is no evidence that Neandertals contributed their mtDNA to modern humans.

However, while mtDNA is extremely informative, it is only a single genetic locus and hence may not reflect the entire genome. With the development of powerful new methods for sequencing DNA, it became possible to obtain a whole genome sequence from a Neandertal (Green et al., 2010), and thus to examine if there is any indication of any genetic contribution from Neandertals to modern humans. Three different analyses were used to address this question, based on different predictions as to what would be found in the genomes of modern humans if their ancestors had interbred with Neandertals. All three analyses gave the same answer: there is a consistent signal of about 1–4% Neandertal DNA in the genome of every non-African studied, but not in the genome of any African studied (Green et al., 2010).

Although this result was widely hailed as indicating that the ancestors of modern humans had indeed interbred with Neandertals, there is another potential explanation for the signal of Neandertal ancestry in the genomes of non-African AMH, namely ancient substructure in African populations (Durand et al., 2011; Green et al., 2010). The idea is that since Neandertals have descended from an earlier migration from Africa, if the same African population that gave rise to Neandertals also later gave rise to the AMH that migrated out of Africa, then Neandertals and non-African AMH are expected to share some ancestry because they stem from the same African source population. The analyses that were performed in the Neandertal genome study (Green et al., 2010) do not distinguish between these two possible explanations. However, approaches were subsequently developed that could distinguish between these competing explanations of Neandertal interbreeding versus ancient substructure in Africa, and these all unequivocally indicated that Neandertal interbreeding was the most likely explanation (Sankararaman et al., 2012; Yang et al., 2012). Thus, the conclusion is that all modern non-African human populations seem to be descended from a single non-African population that interbred with Neandertals, and this conclusion is reinforced by an additional, high-quality Neandertal genome sequence (Prufer et al., 2014). Hence, the spread of AMH from Africa did not involve complete replacement of the non-African archaic humans; Neandertal genes live on in modern populations, and so the RAO-R model is rejected in favor of the RAO-A model.

OTHER ARCHAIC HUMAN GENOMES

During the course of screening fossils that might be suitable for Neandertal genome sequencing, a portion of a fingertip bone from Denisova Cave in Southern Siberia was analyzed. Remarkably, the mtDNA sequence from this fossil revealed that it was neither from a modern human nor from a Neandertal, but rather from something different (Krause et al., 2010). The complete genome sequence was subsequently obtained, and revealed that the population represented by this fossil—called Denisovans—was a sister group to Neandertals—that is, Denisovans and Neandertals both descend from a common ancestor that is more distantly related to modern humans (Reich et al., 2010). In addition to the fingertip bone, the only other currently known fossils of Denisovans are a few teeth; thus, what little we know of Denisovans comes largely from the genome sequence, which was subsequently much improved in quality due to additional improvements in extracting and sequencing ancient DNA (Meyer et al., 2012).

Did Denisovans contribute any ancestry to AMH? Comparison of the Denisovan genome sequence to a worldwide sample of modern humans indicated that ~4–8% Denisovan DNA is found in populations from New Guinea and Bougainville, but nowhere else (Reich et al., 2010). This result is quite surprising, as Denisova Cave is over 7000 km from New Guinea. A follow-up study confirmed this result (Reich et al., 2011), and the implications are discussed in more detail later in this chapter. The important conclusion is that we see evidence of ancestry in AMH from both archaic humans from which we have genomic data (namely, Neandertals and Denisovans), providing further support for the RAO-A model of human origins. Moreover, the archaic genomes provide some extremely useful insights into other aspects of AMH (beyond the sexual habits of our ancestors); archaic ancestry is a source of information about the dispersals of AMH, and about particular genes that were subject to positive selection during the evolution of AMH; I turn now to a discussion of these topics.

ARCHAIC GENOMES AND MODERN HUMAN DISPERSALS

We have previously seen that all non-African AMH carry a similar signal of Neandertal ancestry. This result strongly implies that there was a single major dispersal of AMH from Africa that met and interbred with Neandertals shortly after leaving Africa. Where and when this interbreeding

took place is still a matter of conjecture; however the Near East is viewed as a likely place, as it is close to Africa and fossils of both Neandertals and early AMH have been found there. Some attempts have been made to date the interbreeding, and these indicate dates of about 60–70 Ka, with large confidence intervals (Fu et al., 2014; Sankararaman et al., 2012), consistent with other genetic evidence for the dispersal of AMH from Africa.

Given that interbreeding took place between AMH and Neandertals at least once, it seems likely that additional interbreeding events must have occurred. The current maps of the distribution of Neandertal ancestry in modern human genomes are too crude to allow this question to be addressed, but further refinements—as well as additional Neandertal genome sequences—should permit an estimate of the number of different interbreeding events that are represented by traces of Neandertal ancestry in AMH genomes. Indeed, the finding that Oase 1, an early AMH fossil from Romania, had high amounts of Neandertal ancestry but apparently did not contribute to the ancestry of modern Eurasians, already indicates an additional episode of interbreeding (Fu et al., 2015).

Moreover, studies indicate that East Asians have a small amount of additional Neandertal ancestry (on the order of 0.5–1%) compared to Europeans (Prufer et al., 2014; Wall et al., 2013). This result seems counterintuitive, as Neandertals overlapped with AMH for a longer period of time in Europe than in Asia and thus there should have been more opportunity for interbreeding in Europe. A potential explanation is that there was stronger selection against Neandertal ancestry in European genomes than in East Asian genomes; according to this explanation, ancestral populations of Europeans and East Asians started with the same amount of Neandertal ancestry, but selection removed more Neandertal ancestry from Europeans than from Asians, resulting in more Neandertal ancestry in East Asians than in Europeans. However, other studies refute this explanation, and instead favor additional interbreeding between Neandertals and the ancestors of East Asians (Kim and Lohmueller, 2015; Vernot and Akey, 2015); where, when, and how many times this interbreeding might have occurred is presently a matter for conjecture.

The Denisovan ancestry in AMH has also been investigated in more detail, and used to make inferences about AMH dispersals. The original study that found that Denisovan DNA was limited to populations from New Guinea and Bougainville included only a sparse sampling of populations from East Asia, no populations from island Southeast Asia, and only these two populations from Oceania. It thus became of interest to survey additional populations from Southeast Asia and Oceania for signals of Denisovan ancestry, and a follow-up study was carried out of genome-wide data from across Southeast Asia and Oceania (Reich et al., 2011). This study found significant evidence of Denisovan admixture in another population from New Guinea; aboriginal Australians; several groups from Eastern Indonesia; Fiji and Polynesia; and a Philippine Negrito group, the Mamanwa. However, no evidence of Denisovan gene flow was found in populations from western Indonesia, mainland East Asia, or South Asia (Reich et al., 2011).

The Australians and New Guineans possess similar levels of Denisovan DNA (about 4–8%), consistent with a common ancestry for Australians and New Guineans (McEvoy et al., 2011). Many of the other groups that show Denisova admixture are thought to have recent ancestry and/or gene flow from New Guinea (in particular, Eastern Indonesia, Fiji, and Polynesia), which raises the question as to whether the Denisova admixture in these groups could be explained by shared ancestry—and hence a shared signal of Denisova admixture—with New Guinea. To test this hypothesis, the amount of New Guinea ancestry was estimated for each population showing significant evidence of Denisova admixture (Reich et al., 2011). The predicted outcome of this analysis is that if New Guinea ancestry is accounting for the signal of Denisova admixture in a population, then the amount of New Guinea ancestry should be correlated with the amount of Denisova admixture. The results of this analysis showed that for all of the Eastern Indonesian groups, Fiji, and Polynesia, the amount of Denisova admixture was indeed correlated with the amount of New Guinea ancestry. Thus, as expected from previous studies showing New Guinea ancestry in these groups (Kayser et al., 2006; Mona et al., 2009), shared New Guinea ancestry accounts for their Denisova admixture signal. However, the Philippine Negrito group, the Mamanwa, have significant Denisova admixture but no detectable New Guinea ancestry. Hence, recent ancestry or gene flow from New Guinea does not account for the Denisova admixture in the Mamanwa.

Important information can also be gleaned from populations who do not show significant evidence of Denisova gene flow. In particular, there is no evidence of Denisova gene flow in two groups thought to be related to the Mamanwa, New Guineans, and Australians: a Malaysian Negrito group, the Jehai; and in the Andamanese Onge (Reich et al., 2011). A modeling approach called Admixture Graph Analysis (Reich et al., 2009) was then applied to the data, to come up with a model of population history that best explains all of these results. In Admixture Graph Analysis, various statistics are estimated from the genome-wide data as well as from a graph that represents the divergence pattern and gene flow between the populations; the graph that provides the best fit between the observed data and the statistics estimated from the model is taken as the most likely model of population history. The results from applying Admixture Graph Analysis to the genome-wide data (Reich et al., 2011) indicate that the ancestors

of the Onge, Jehai, Mamanwa, Australians, and New Guineans are all descended from an earlier migration to Southeast Asia and Near Oceania than are the ancestors of all other East and Southeast Asians (Fig. 4.2). The ancestors of the Onge and Jehai diverged first, followed by admixture with Denisovans in a population that was ancestral to the Mamanwa, Australians, and New Guineans. The Mamanwa then diverged, followed by divergence between Australians and New Guineans. This was followed by a second dispersal to East and Southeast Asia, and the ancestors of this second dispersal also admixed heavily with the Jehai and Mamanwa, but not the Onge (Reich et al., 2011).

This scenario, while by no means proven, strongly supports multiple dispersals to Asia and Oceania. The number of dispersals to Asia and Oceania has been disputed by researchers; some studies have argued for multiple dispersals (Lahr and Foley, 1994), while others have argued for a single major dispersal of modern humans to this region (Abdulla et al., 2009). The admixture signals in modern humans from Denisovans argue strongly for multiple dispersals. Another analysis of genome-wide data from populations from Asia and New Guinea, which was not based on admixture with extinct hominins but instead used a different approach to fit a model of population history to the genome-wide data, also concluded that the best-fitting model involved multiple dispersals (Wollstein et al., 2010). Moreover, an analysis of the genome sequence of an aboriginal Australian, obtained from 100-year-old hairs, also supports separate dispersals of Australians and East Asians (Rasmussen et al., 2011). The current evidence from genome-wide studies thus strongly and convincingly supports multiple dispersals of modern humans to Asia and Oceania.

The second implication of the scenario outlined above is that it implies that admixture with Denisovans most likely

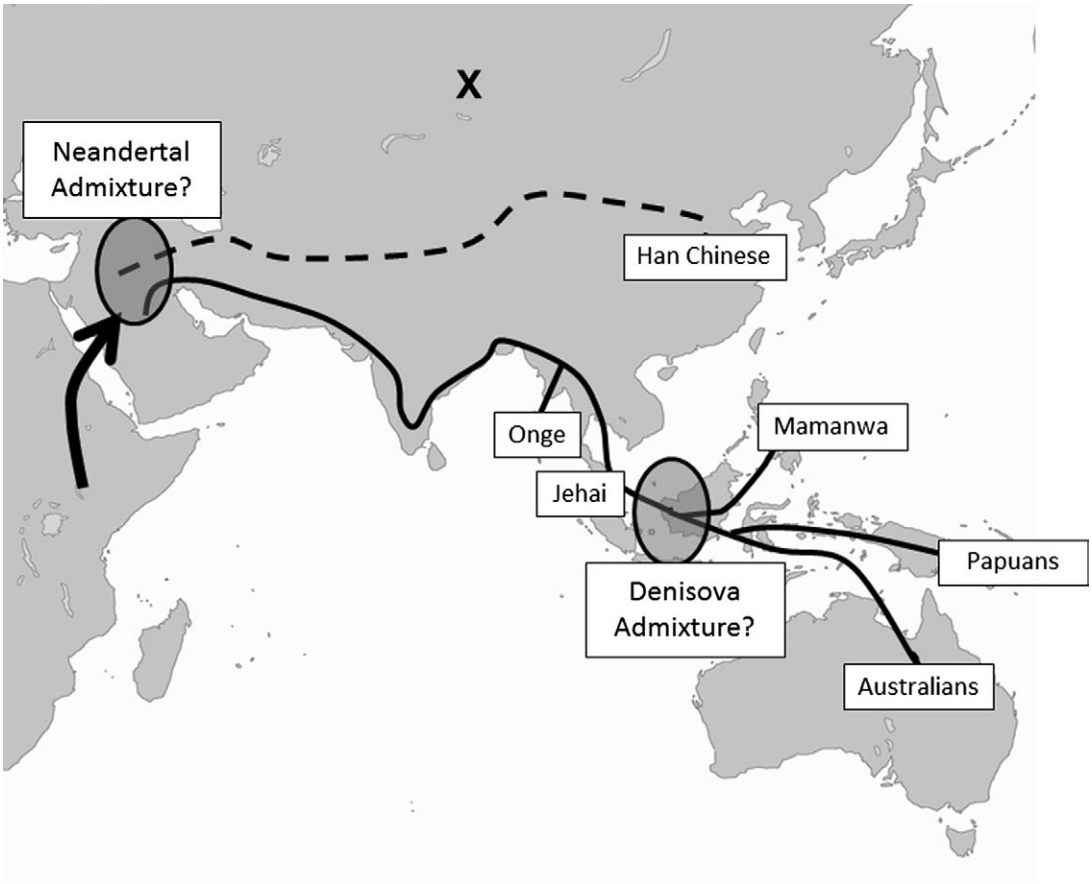

FIGURE 4.2 A putative scenario depicting human migration history as revealed by signals of archaic human admixture (Reich et al., 2011). The X marks the location of Denisova Cave. Modern humans arise in Africa, migrate from Africa, and soon after, admix with Neandertals. This is followed by a dispersal from this non-African source population that presumably followed a southern route (*solid line*) as the first populations to diverge are ancestors of the Onge and Jehai. There is then admixture with Denisovans, followed by divergence of the ancestors of the Mamanwa, Australians, and Papuans. The ancestors of other east Asian populations, such as Han Chinese, are descended from subsequent migrations from this non-African source population, perhaps along a more northerly route (*dashed line*). *This figure first appeared in, and is re-used with permission from: Stoneking, M., 2016. Archaic genomes and the peopling of South Asia. In: Schug, G.R., Walimbe, S. (Eds.), A Companion to South Asia in the Past, Wiley-Blackwell.*

TABLE 4.1 Genes Exhibiting Potential Signals of Adaptive Introgression

Candidate Gene	Archaic Source	AMH Populations Influenced	Gene Function	Putative Reason for Selection	References
HLA A, B, C	N, D	Eurasians, Oceanians	Immune response	Disease resistance	Abi-Rached et al. (2011)
STAT2	N	Oceanians	Immune response	Disease resistance	Mendez et al. (2012)
OAS2	N	Europeans	Immune response	Disease resistance	Sankararaman et al. (2014)
SLC16A11	N	Native Americans	Lipid metabolism	Diet	SIGMA Type 2 Diabetes Consortium (2014)
EPAS1	D	Tibetans	Hypoxia response	High altitude	Huerta-Sanchez et al. (2014)
HYAL2	N	East Asians	UV response	Skin pigmentation	Ding et al. (2014)

AMH, Anatomically modern human; *N,* Neandertal; *D,* Denisovan.

occurred somewhere in the eastern islands in Southeast Asia. If that is indeed the case, then Denisovans were spread across an enormous geographic and environmental range. Denisova Cave is some 7000–8000 km from where the admixture is inferred to have occurred with modern humans (Fig. 4.2), and this range encompasses environments that range from the taiga forests of Southern Siberia to tropical Southeast Asia. The inference is that Denisovans must have been capable of existing in a wide variety of environments—more so than any other hominin known to date, with the exception of our own species. Thus, the admixture analysis not only informs us about modern humans, but also sheds some light on the abilities of the Denisovans.

However, studies have added further layers of complication to the already complicated picture in Fig. 4.2. It now appears that Denisovan ancestry is much more widespread across East Asia and extends into the Americas, at a barely detectable level of ~0.2% (Prufer et al., 2014; Skoglund and Jakobsson, 2011). Moreover, this widespread East Asian Denisovan ancestry appears to be related to the Denisovan ancestry that is at higher frequency in Oceania (Qin and Stoneking, 2015). There are two potential scenarios that could account for these results. First, a population ancestral to East Asians and Oceanians interbred somewhere with Denisovans and then spread across East Asia and Oceania. This was followed by a later migration to East Asia of people without Denisovan ancestry; these people interbred with the East Asians and thereby reduced the amount of their Denisovan ancestry, but this migration did not extend to Oceania, and so Oceanians retain the higher signal of Denisovan ancestry. Second, a population ancestral specifically to Oceanians interbred with Denisovans (eg, as depicted in Fig. 4.2) and then there was a back-migration to East Asia whose descendants interbred with East Asian populations, thereby contributing a smaller amount of Denisovan ancestry. Further work—in particular, whole genome sequences—will be needed to distinguish between these two scenarios.

ARCHAIC GENOMES AND SELECTION

In addition to providing information about migrations, the archaic genomes have been a source of insights into genes that have been subject to positive selection during the origin and dispersal of AMH. The basic idea is that if one looks at the landscape of archaic human ancestry across the chromosomes of AMH genomes, one can identify "deserts" and "islands" of archaic ancestry (Sankararaman et al., 2014; Vernot and Akey, 2014). That is, in the absence of selection, archaic ancestry should be distributed at random across the chromosomes of an individual. However, a chromosomal region that is significantly depauperate in archaic ancestry (when analyzing many individuals from a population; there is not enough information in the genome of a single individual to carry out this analysis) could indicate that the archaic form of some gene(s) in this region were selected against, presumably because the AMH form had a significant selective advantage. Thus, genes important in the evolution of AMH may reside in such deserts of archaic ancestry. Conversely, there may also be chromosomal regions which have significantly more archaic ancestry (again, when analyzing many individuals) than would be expected if archaic ancestry is distributed randomly across chromosomal regions. These islands of archaic ancestry may harbor gene(s) for which the archaic form conferred a significant selective advantage in AMH.

Currently, the methods for accurately identifying such genomic deserts and islands are still in their infancy. However, some intriguing signals have been identified. For example, one desert of Neandertal ancestry in the genomes of all non-Africans contains a gene called *FOXP2* (Vernot and Akey, 2014). Defects in this gene interrupt the normal production of speech (Lai et al., 2001), and while AMH and Neandertals share the same form of the *FOXP2* protein, there may be significant differences in the regulation of *FOXP2* gene expression between AMH and Neandertals (Maricic et al., 2013). It is thus tempting to speculate that there may have been important differences in speech production (or related cognitive abilities) between Neandertals and AMH, but currently this is just speculation.

There are, however, some very intriguing cases where it does appear that the archaic form of a gene was contributed to some AMH population(s) by interbreeding and subsequently was selected for because it conferred some advantage. These cases are summarized in Table 4.1 and include a few surprises as well as some that make more sense. An example of a very surprising finding is that the form of a gene called *EPAS1*, which is associated with adaptation to high altitude in Tibetans (Simonson et al., 2010; Yi et al., 2010), appears to have come from Denisovans (Huerta-Sanchez et al., 2014). How this came about is still a matter of conjecture, but may certainly indicate that interbreeding with Denisovans occurred over a wider area than initially suspected, as discussed previously. A finding that is less surprising is that some genes associated with resistance/susceptibility to infectious diseases seem to have been contributed from both Neandertals and Denisovans to some AMH populations (Table 4.1). If one thinks about it, this "adaptive introgression" (Racimo et al., 2015) does make sense: after all, the ancestors of Neandertals and Denisovans spread out of Africa hundreds of thousands of years ago, spread across the Old World, and were successful in adapting genetically to the new environments, climates, diseases, parasites, sources of nutrition, etc., that they encountered. Then, 60–90 Ka, our ancestors start spreading out of Africa and have to do the same thing all over again. So if by interbreeding with archaic humans the AMH ancestors were able to pick up genes that helped them adapt to the new circumstances out of Africa, this would have given them a leg up. Who knows: maybe in the absence of such interbreeding, our ancestors would not have been able to survive out of Africa. This is admittedly pure speculation, but for sure the advantageous genes contributed to our ancestors by interbreeding with archaic humans must have benefitted our ancestors—otherwise, we would not see the significant signals of positive selection associated with such genes.

CONCLUDING REMARKS

In summary, the overall picture of recent human evolution is not one of long-term continuity and isolation, but rather multiple events of migration and interbreeding, the latter involving not just AMH and archaic humans, but also among various AMH populations (Pugach and Stoneking, 2015). It is quite likely that every human population, including African populations, which probably interbred with some as-yet-unknown archaic human(s) (Hammer et al., 2011), has some history of interbreeding. The fact that humans have such a long history of migration is perhaps an important fact that governments grappling with current issues surrounding migration and immigration would do well to remember; the spread of our own species across and out of Africa, and the ensuing contacts with archaic humans, may have been the first migration "problem."

ACKNOWLEDGMENTS

I thank my students and colleagues—in particular, the members of the Neandertal Genome Sequence Consortium and the Denisova Genome Sequence Consortium—for carrying out the work described herein and for useful and enlightening discussions. Research by my laboratory is supported by the Max Planck Society.

REFERENCES

Abdulla, M.A., Ahmed, I., Assawamakin, A., et al., 2009. Mapping human genetic diversity in Asia. Science 326, 1541–1545.

Abi-Rached, L., Jobin, M.J., Kulkarni, S., et al., 2011. The shaping of modern human immune systems by multiregional admixture with archaic humans. Science 334, 89–94.

Briggs, A.W., Good, J.M., Green, R.E., et al., 2009. Targeted retrieval and analysis of five Neandertal mtDNA genomes. Science 325, 318–321.

Cann, R.L., Stoneking, M., Wilson, A.C., 1987. Mitochondrial DNA and human evolution. Nature 325, 31–36.

Ding, Q., Hu, Y., Xu, S., et al., 2014. Neanderthal introgression at chromosome 3p21.31 was under positive natural selection in East Asians. Molecular Biology and Evolution 31, 683–695.

Durand, E.Y., Patterson, N., Reich, D., Slatkin, M., 2011. Testing for ancient admixture between closely related populations. Molecular Biology and Evolution 28, 2239–2252.

Fagundes, N.J., Ray, N., Beaumont, M., et al., 2007. Statistical evaluation of alternative models of human evolution. Proceedings of the National Academy of Sciences of the United States of America 104, 17614–17619.

Fu, Q., Hajdinjak, M., Moldovan, O.T., et al., 2015. An early modern human from Romania with a recent Neanderthal ancestor. Nature 524 (7564), 216–219 (accepted).

Fu, Q., Li, H., Moorjani, P., et al., 2014. Genome sequence of a 45,000-year-old modern human from western Siberia. Nature 514, 445–449.

Garrigan, D., Mobasher, Z., Severson, T., et al., 2005. Evidence for archaic Asian ancestry on the human X chromosome. Molecular Biology and Evolution 22, 189–192.

1000 Genomes Consortium, 2012. An integrated map of genetic variation from 1,092 human genomes. Nature 491, 56–65.

Green, R.E., Krause, J., Briggs, A.W., et al., 2010. A draft sequence of the Neandertal genome. Science 328, 710–722.

Hammer, M.F., Woerner, A.E., Mendez, F.L., et al., 2011. Genetic evidence for archaic admixture in Africa. Proceedings of the National Academy of Sciences of the United States of America 108, 15123–15128.

Harding, R.M., Fullerton, S.M., Griffiths, R.C., et al., 1997. Archaic African and Asian lineages in the genetic ancestry of modern humans. The American Journal of Human Genetics 60, 772–789.

Harris, E.E., Hey, J., 1999. X chromosome evidence for ancient human histories. Proceedings of the National Academy of Sciences of the United States of America 96, 3320–3324.

Huerta-Sanchez, E., Jin, X., Asan, et al., 2014. Altitude adaptation in Tibetans caused by introgression of Denisovan-like DNA. Nature 512, 194–197.

Ingman, M., Kaessmann, H., Paabo, S., Gyllensten, U., 2000. Mitochondrial genome variation and the origin of modern humans. Nature 408, 708–713.

Kayser, M., Brauer, S., Cordaux, R., et al., 2006. Melanesian and Asian origins of Polynesians: mtDNA and Y chromosome gradients across the Pacific. Molecular Biology and Evolution 23, 2234–2244.

Kim, B.Y., Lohmueller, K.E., 2015. Selection and reduced population size cannot explain higher amounts of Neandertal ancestry in East Asian than in European human populations. The American Journal of Human Genetics 96, 454–461.

Krause, J., Fu, Q., Good, J.M., et al., 2010. The complete mitochondrial DNA genome of an unknown hominin from southern Siberia. Nature 464, 894–897.

Krings, M., Stone, A., Schmitz, R.W., et al., 1997. Neandertal DNA sequences and the origin of modern humans. Cell 90, 19–30.

Lahr, M., Foley, R., 1994. Multiple dispersals and modern human origins. Evolutionary Anthropology 3, 48–60.

Lai, C.S., Fisher, S.E., Hurst, J.A., et al., 2001. A forkhead-domain gene is mutated in a severe speech and language disorder. Nature 413, 519–523.

Li, J.Z., Absher, D.M., Tang, H., et al., 2008. Worldwide human relationships inferred from genome-wide patterns of variation. Science 319, 1100–1104.

Maricic, T., Gunther, V., Georgiev, O., et al., 2013. A recent evolutionary change affects a regulatory element in the human FOXP2 gene. Molecular Biology and Evolution 30, 844–852.

McEvoy, B.P., Lind, J.M., Wang, E.T., et al., 2011. Whole-genome genetic diversity in a sample of Australians with deep Aboriginal ancestry. The American Journal of Human Genetics 87, 297–305.

Mendez, F.L., Watkins, J.C., Hammer, M.F., 2012. A haplotype at STAT2 Introgressed from Neanderthals and serves as a candidate of positive selection in Papua New Guinea. The American Journal of Human Genetics 91, 265–274.

Meyer, M., Kircher, M., Gansauge, M.T., et al., 2012. A high-coverage genome sequence from an archaic Denisovan individual. Science 338, 222–226.

Mona, S., Grunz, K.E., Brauer, S., et al., 2009. Genetic admixture history of Eastern Indonesia as revealed by Y-chromosome and mitochondrial DNA analysis. Molecular Biology and Evolution 26, 1865–1877.

Pakendorf, B., Stoneking, M., 2005. Mitochondrial DNA and human evolution. Annual Review of Genomics and Human Genetics 6, 165–183.

Prufer, K., Racimo, F., Patterson, N., et al., 2014. The complete genome sequence of a Neanderthal from the Altai Mountains. Nature 505, 43–49.

Prugnolle, F., Manica, A., Balloux, F., 2005. Geography predicts neutral genetic diversity of human populations. Current Biology 15, R159–R160.

Pugach, I., Stoneking, M., 2015. Genome-wide insights into the genetic history of human populations. Investigative Genetics 6, 6.

Qin, P., Stoneking, M., 2015. Denisovan ancestry in East Eurasian and Native American populations. Molecular Biology and Evolution 32, 2665–2674.

Racimo, F., Sankararaman, S., Nielsen, R., Huerta-Sanchez, E., 2015. Evidence for archaic adaptive introgression in humans. Nature Reviews Genetics 16, 359–371.

Rasmussen, M., Guo, X., Wang, Y., et al., 2011. An Aboriginal Australian genome reveals separate human dispersals into Asia. Science 334, 94–98.

Reich, D., Green, R.E., Kircher, M., et al., 2010. Genetic history of an archaic hominin group from Denisova Cave in Siberia. Nature 468, 1053–1060.

Reich, D., Patterson, N., Kircher, M., et al., 2011. Denisova admixture and the first modern human dispersals into Southeast Asia and Oceania. The American Journal of Human Genetics 89, 516–528.

Reich, D., Thangaraj, K., Patterson, N., et al., 2009. Reconstructing Indian population history. Nature 461, 489–494.

Rosenberg, N.A., Pritchard, J.K., Weber, J.L., et al., 2002. Genetic structure of human populations. Science 298, 2381–2385.

Sankararaman, S., Mallick, S., Dannemann, M., et al., 2014. The genomic landscape of Neanderthal ancestry in present-day humans. Nature 507, 354–357.

Sankararaman, S., Patterson, N., Li, H., et al., 2012. The date of interbreeding between Neandertals and modern humans. PLoS Genetics 8, e1002947.

Sigma Type 2 Diabetes Consortium, 2014. Sequence variants in SLC16A11 are a common risk factor for type 2 diabetes in Mexico. Nature 506, 97–101.

Simonson, T.S., Yang, Y., Huff, C.D., et al., 2010. Genetic evidence for high-altitude adaptation in Tibet. Science 329, 72–75.

Skoglund, P., Jakobsson, M., 2011. Archaic human ancestry in East Asia. Proceedings of the National Academy of Sciences of the United States of America 108, 18301–18306.

Stoneking, M., 2008. Human origins. The molecular perspective. EMBO Report 9 (Suppl. 1), S46–S50.

Stoneking, M., Krause, J., 2011. Learning about human population history from ancient and modern genomes. Nature Reviews Genetics 12, 603–614.

Stringer, C.B., Andrews, P., 1988. Genetic and fossil evidence for the origin of modern humans. Science 239, 1263–1268.

Underhill, P.A., Shen, P., Lin, A.A., et al., 2000. Y chromosome sequence variation and the history of human populations. Nature Genetics 26, 358–361.

Vernot, B., Akey, J.M., 2014. Resurrecting surviving Neandertal lineages from modern human genomes. Science 343, 1017–1021.

Vernot, B., Akey, J.M., 2015. Complex history of admixture between modern humans and Neandertals. The American Journal of Human Genetics 96, 448–453.

Vigilant, L., Stoneking, M., Harpending, H., et al., 1991. African populations and the evolution of human mitochondrial DNA. Science 253, 1503–1507.

Wall, J.D., Hammer, M.F., 2006. Archaic admixture in the human genome. Current Opinion in Genetics & Development 16, 606–610.

Wall, J.D., Yang, M.A., Jay, F., et al., 2013. Higher levels of Neanderthal ancestry in East Asians than in Europeans. Genetics 194, 199–209.

Wollstein, A., Lao, O., Becker, C., et al., 2010. Demographic history of Oceania inferred from genome-wide data. Current Biology 20, 1983–1992.

Wolpoff, M.H., Wu, X.Z., Thorne, A.G., 1984. Modern *Homo sapiens* origins: a general theory of hominid evolution involving the fossil evidence from east Asia. In: Spencer, F.H., Smith, F. (Eds.), The Origins of Modern Humans. Alan R. Liss, New York, pp. 411–483.

Yang, M.A., Malaspinas, A.S., Durand, E.Y., Slatkin, M., 2012. Ancient structure in Africa unlikely to explain Neanderthal and non-African genetic similarity. Molecular Biology and Evolution 29, 2987–2995.

Yi, X., Liang, Y., Huerta-Sanchez, E., et al., 2010. Sequencing of 50 human exomes reveals adaptation to high altitude. Science 329, 75–78.

Chapter 5

World Dispersals and Genetic Diversity of Mankind: The Out-of-Africa Theory and Its Challenges

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INTRODUCTION

A human individual is born, perhaps moves around during her or his lifetime, perhaps has children a few times, and ultimately dies. The existence of the human species, however, transcends that of a human individual in both time and space. The total human population has a continuous turnover of individuals as some die and others are born. Through reproduction, the population persists over time for periods far longer than that of any individual. Because the population consists of many individuals at any given time, the population can exist over a wide geographical space that is far greater than the space that any individual will live in during his or her lifetime. Each human individual also bears three genomes: one nuclear genome inherited from the father, another nuclear genome from the mother, and a mitochondrial genome from the mother. This genetic material also has an existence in both space and time that transcends the individuals that temporally bear it. Because DNA can replicate, the genes found in an individual's genomes have come from the past and can be passed on to the future. The individual is mortal, but her or his genes can travel into the future through replication and reproduction. Because of DNA replication, several identical copies of a specific type of gene can simultaneously exist in multiple individuals. Although an individual can only be at one place at one time, the identical copies of the genes that this individual bears can be at many places at one time. Hence, a gene's existence transcends that of an individual in time and space. The fate of human genes through time and space is the primary concern of this chapter.

Genes do not move through space on their own, but rather depend upon individuals to move them. Biological dispersal is the movement of individuals (and in some species, their gametes) that has the potential for moving genes through space; that is, an individual disperses when he or she moves from their place of birth to other places where they might reproduce, thereby causing the movement of genes. The movement of gene copies through space across generations is called gene flow.

Gene flow can occur through individual dispersal, but in social species such as humans, individuals often disperse as part of a larger group. This group could be a family, a clan, a tribe, or even some larger group. Dispersal of populations of humans also results in gene flow and can greatly amplify the magnitude of that gene flow beyond what a single individual dispersing would cause. When populations disperse, they sometimes come into contact with other populations with which there had been little or no previous gene flow for many generations. When populations have little or no gene flow for many generations, they tend to become genetically differentiated. Mutations that arose in one population may be absent from the other. The sampling effects associated with Mendelian inheritance cause random changes in the frequencies of even those genes shared by both populations—a phenomenon called genetic drift. Finally, natural selection can only operate upon the genetic variation available in the gene pool of the population, so differences caused by mutation and genetic drift can be amplified by natural selection. This is particularly important when the dispersing population had previously inhabited a different environment that favored different local adaptations through natural selection. When

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00005-3

population dispersal results in two or more genetically differentiated populations to come into contact, interbreeding between these populations can ensue. The gene flow caused by interbreeding between previously genetically differentiated populations is called admixture. An alternative to admixture when populations meet is that one population drives the other to extinction without any interbreeding. This process is called replacement.

The basic models of human evolution over the last 2 million years are primarily defined by the hypothesized patterns, amounts and timing of individual and population dispersal, gene flow, admixture, and replacement. There is a strong consensus that the human lineage originally evolved in Sub-Saharan Africa and remained there until the expansion of *Homo erectus* populations out of Africa into Eurasia about 1.9 to 1.8 Ma. The models differ in the events that occurred after that original expansion of *H. erectus* out of Africa.

The "classic" model of human evolution that was popular in the first half of the 20th century is that the Old World hominin populations subdivided into many divergent evolutionary branches, with one branch expanding out into the regions inhabited by the others, driving them to complete extinction (Dobzhansky, 1944). Some anthropologists regarded these regional branches as so divergent as to constitute different species of humans (Howells, 1942). The classic model has no role for gene flow or admixture, only for population dispersal and replacement. At first it was not clear which regional branch of humanity was the "winner," but subsequent fossil finds indicated that many anatomical features associated with living humans first arose in Sub-Saharan Africa and only later spread out of Africa. Accordingly, the classic model became the out-of-Africa replacement (OAR) model (Stringer and Andrews, 1988). This model posits that anatomically modern humans arose first in Sub-Saharan Africa, and then around 60,000 to 70,000 years ago (although some argue for 100,000 to 130,000 years ago), expanded out of Africa, driving to complete extinction all the other human populations encountered in Eurasia (Fig. 5.1A). The modern populations that replaced the archaic Eurasian populations then split into the modern "races." This modern version of the classic model also has no role for gene flow or admixture, only population dispersal and replacement. It also predicts that all living humans trace all of their genetic ancestry to Sub-Saharan Africa, with no genetic input at all from other regions of the Old World.

In the 1940s, Weidenreich proposed the multiregional hypothesis (Fig. 5.1B) as an alternative to the classic model (Weidenreich, 1946). The multiregional model posits that human populations living in both Africa and Eurasia evolved into their modern forms as a single species, with gene flow interconnecting them throughout the process. Consequently, there is no evolutionary tree of human populations, as in the classic model (Fig. 5.1A), but rather a trellis indicating genetically interconnected regional populations. These regional populations still showed local genetic differentiation due to the gene flow being restricted and/or natural selection for local adaptation. Even under restricted gene flow, a mutation arising anywhere in the Old World could spread to all populations, particularly if it were selected. In great contrast to the OAR hypothesis, there is no single place of origin for living humans, but rather living humans represent a genetic amalgam from many ancestral regions. Gene flow is a major evolutionary force in the multiregional model.

The diametric opposite of the multiregional model is the candelabra model (Fig. 5.1C; Coon, 1962). This model posits that the human populations established in Africa, Europe, and Asia at the time when *H. erectus* became fragmented from one another, with no gene flow or admixture, just as with the OAR model. However, there was no replacement; instead, each regional population evolved independently into a modern race of living humans in the same geographical regions that they inhabited throughout the Pleistocene. Hence, as with the classic model, there is no role for gene flow or admixture, but unlike the classic model there is also no role for population dispersal and replacement. The candelabra model is also similar to the classic model in positing that the modern races of humans are separate branches on an evolutionary tree, but the time of separation differs greatly in these two models. In the OAR model, this split is relatively recent; in the candelabra model this split occurred at the time of the expansion of *H. erectus* out of Africa, now regarded as about 1.9 to 1.8 Ma. However, because the candelabra model also posited a multiregional ancestry for living humans, it has also frequently been called a "multiregional" model. This dual use of the word multiregional has caused great confusion. Theodosius Dobzhansky, a great population geneticist and one of the major architects of the 20th century evolutionary synthesis, attempted to clarify the evolutionary difference between the Weidenreich multiregional model and the candelabra model. Dobzhansky (1944) argued for the implausibility of the candelabra model and even the classic model on the basis of their assumption of complete reproductive isolation for 1 million years or more, with the candelabra model being particularly implausible from an evolutionary perspective as it required an extremely unlikely degree of parallel evolution during the evolution of human modernity from a *H. erectus*—like ancestor. Dobzhansky came down on the side of Weidenreich's model on the basis of these population genetic principles because gene flow would eliminate the need for parallel evolution and the unlikely persistence of reproductive

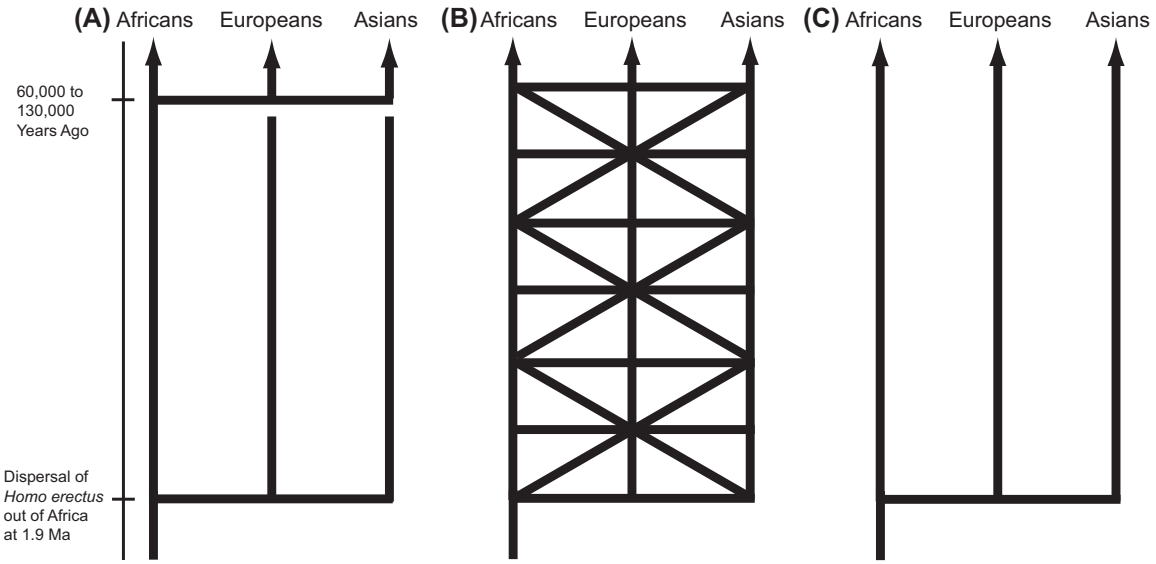

FIGURE 5.1 Three models of human evolution. All three models show that the human lineage was confined to Africa until about 1.9 Ma, when *Homo erectus* expanded into Eurasia. In the out-of-Africa replacement model, Panel A, humanity then split into three branches. Anatomically modern humans evolved in the African branch, which then spread out-of-Africa into Eurasia between 60,000 and 130,000 years ago. All the archaic Eurasian populations were driven to complete genetic extinction, indicated by the broken branches in Eurasia. In Weidenreich's multiregional model, Panel B, the African and Eurasian populations were interconnected by gene flow after the expansion of *H. erectus*, as indicated by a trellis-like structure. All humans evolved into modernity together because of gene flow, with no single location being the origin of all modern humans. Panel C shows Coon's candelabra model which posits that humanity split into three branches after the expansion of *H. erectus*, and all three branches independently evolved into their current forms with no gene flow interconnecting them.

isolation over long periods of time. Dobzhansky (1944, p. 262) also argued that, contrary to the classic model, genetic mixing negates the "*a priori* need to assume that the character and gene complexes which are collectively known as the modern species *Homo sapiens* arose in any one place or at any particular time." Instead, the gene complexes of modern humans were put together through gene flow and natural selection from mutations arising in "different parts of the distribution area of a species" (Dobzhansky, 1944, p. 262). However, Dobzhansky was not against the idea of one regional population expanding into the territories of other populations, but he envisioned that such a population expansion would result in admixture, not replacement. In a direct attack on the classic model, Dobzhansky (1944, pp. 262–263) wrote "The conception that the modern *Homo sapiens* arose in some definite place, then spread the world over destroying outright all other hominid strains, and finally split up into races which in turn proceeded to diverge from each other, is probably an oversimplification of the actual story." His concession to the classic model was that "The 'classic' theory is probably justified to the extent that some of the races of the past have contributed more germ plasm than others to the formation of the present humanity" (Dobzhansky, 1944, p. 263). Dobzhansky's suggestion has morphed into what is now known as the "mostly out-of-Africa hypothesis" (Relethford, 2001), which posits that the recent human population expansion out of Africa resulted in limited admixture with Eurasian populations and not complete replacement. Under this model, much, but not all, of our genetic ancestry traces to Sub-Saharan Africa, but there is still a smaller component of Eurasian origin. An even greater role for admixture and gene flow arose from analyses of genetic data that indicated a mid-Pleistocene population expansion from Sub-Saharan Africa into Eurasia that also resulted in admixture, not replacement, and the establishment of restricted gene flow between African and Eurasian populations by the mid-Pleistocene that resulted in a trellis-like structure from that point onwards in human evolution (Fig. 5.2) (Templeton, 2002, 2007, 2013, 2015).

The differences between the models shown in Figs. 5.1 and 5.2 are in the role, timing and location of gene flow, admixture, population dispersal, and replacement. Hence, these are the central issues in addressing the various models of the evolution of modern humanity.

PHYLOGEOGRAPHY AND MODELS OF HUMAN EVOLUTION

Coalescent Theory and Mitochondrial Eve

The models of human evolution shown in Fig. 5.1 were motivated primarily from the fossil record, although theoretical population genetic considerations did play a role in some of these models (Dobzhansky, 1944). As genetic

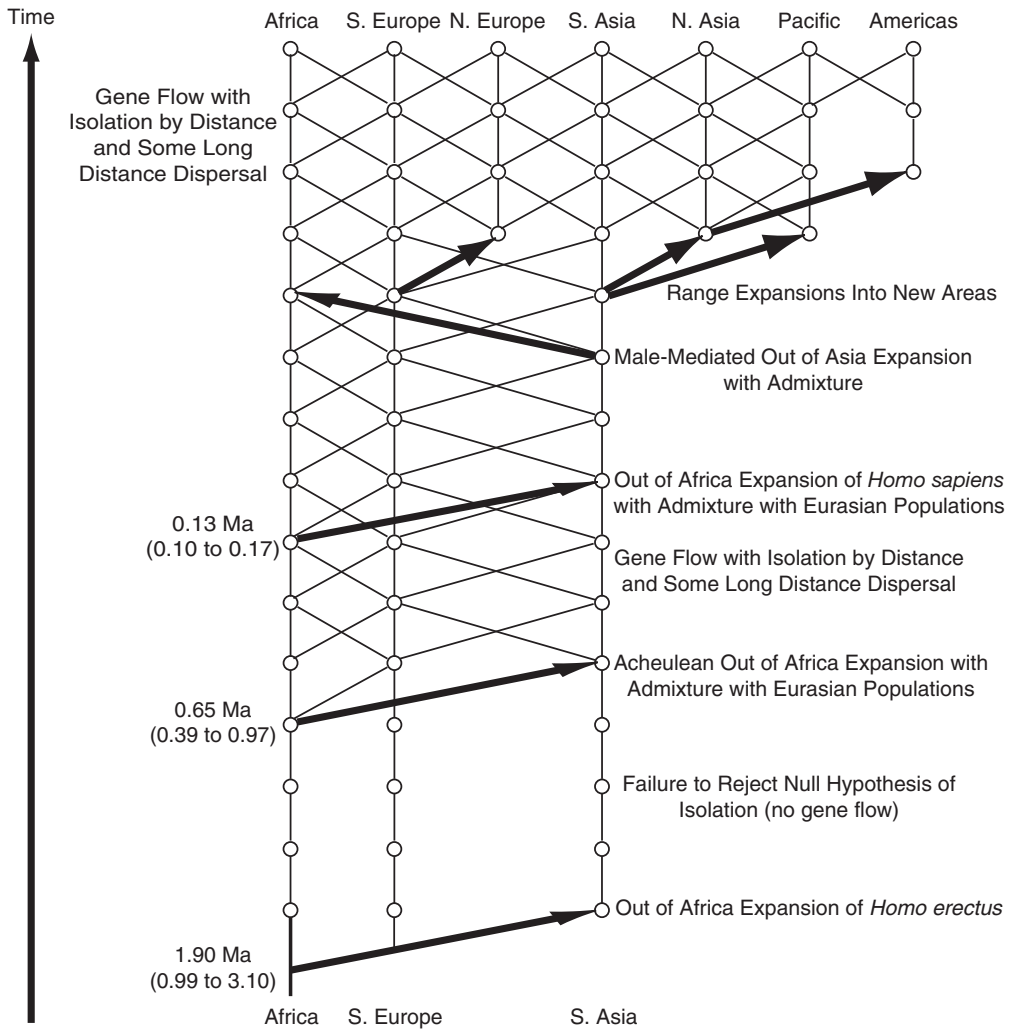

FIGURE 5.2 A model of human evolution arising from statistical hypotheses testing of genomic regions showing little to no recombination. Thin vertical lines indicate genetic descent within a local region, and diagonal lines indicate gene flow between regions. Population expansion events are indicated by thick arrows. No lines of descent are broken by these expansion events as the hypothesis of replacement is always rejected.

technologies developed and became more powerful, genetics began to play an increasingly important role in our understanding of human evolution over the last 2 million years, starting with the landmark publication of a study on mitochondrial DNA variation in living human populations (Cann et al., 1987). Moreover, a new area of theoretical population genetics, known as coalescent theory (Kingman, 1982a,b), had developed that produced a new framework for analyzing DNA variants in the present to understand the past.

As mentioned in the introduction, DNA can replicate and pass on identical copies of itself to the next generation, albeit for the occasional mutation that produces a new genetic variant. A forward perspective of looking toward the next generation dominated the initial modeling of evolution by population geneticists. However, in most evolutionary genetic studies, the DNA that could be surveyed for variation was the DNA sampled from living individuals, with the inferences often being directed toward the past, not the future; that is, how did the evolutionary process create the amount and patterns of genetic variation observed today? The essence of coalescent theory is to look at DNA replication backward in time. When DNA replicates, it produces two copies of itself. But starting with the two copies and looking backward in time, these two DNA molecules "coalesce" into a single DNA molecule. Hence, DNA coalescence is the time-inverse of DNA replication. Any two homologous pieces of DNA observed today coalesced into a single molecule of DNA at some time in the past. Coalescent theory is concerned with the dynamics of the coalescent process in which all the homologous molecules of DNA observed today merge into a single ancestral molecule in the past through a series of coalescent events between DNA lineages. DNA is in

essence a living fossil; each piece of DNA contains many nucleotide sequences that came from previous generations through the process of DNA replication. Some parts of the sequence have changed through the process of mutation and recombination, but coalescent theory allows the current DNA variation to make inferences about the past.

Consider a sample of n copies of a homologous gene that are surveyed from a living population. As one looks backward in time, eventually two of these n DNA lineages will coalesce; that is, a DNA replication event is encountered that produced the two present-day DNA lineages. This coalescent event reduces the number of DNA lineages to $n - 1$. As one looks further and further back in time, additional coalescent events are encountered, each one reducing the number of DNA lineages by one, until finally the n present-day DNA lineages in the original sample coalesce into a single DNA molecule that is the ancestral molecule of all the n DNA copies sampled in the present. The time in generations to coalesce of all n copies of a gene to the common ancestral gene is $2xN_{ef}(1 - 1/n)$ where x is the ploidy level and N_{ef} is the inbreeding effective size (Kingman, 1982a,b). The inbreeding effective size is an idealized parameter in population genetics that measures the power of genetic drift as an evolutionary force. It is *not* the census size of a population. In a species such as humans that has a long history of sustained growth in population size (Coventry et al., 2010), the inbreeding effective size is expected to be much smaller than the census size, often by orders of magnitude (Templeton, 2006).

For a large sample (n large), the expected coalesce time is approximately $2xN_{ef}$. Most genes in the human genome are autosomal, and since we are a diploid species, $x = 2$. Hence, human autosomal genes have an expected time to coalesce for all copies of $4N_{ef}$. Mitochondrial DNA (mtDNA) and Y-chromosomal DNA (Y-DNA) are inherited as a haploid ($x = 1$). In addition, both of these types of DNA are inherited only through one sex; females for mtDNA and males for Y-DNA. The N_{ef} that is applicable to autosomal DNA is not applicable to unisexually inherited DNA. Instead, the expected time to ultimate coalescence of mtDNA is influenced only by the inbreeding effective size of females, say $N_{ef♀}$. Thus, with $x = 1$, the expected coalescence time of mtDNA is $2N_{ef♀}$. Similarly, Y-DNA is inherited as a paternal haploid, so its expected coalescent time is $2N_{ef♂}$, the inbreeding effective size for males. Because the sex ratio is close to 50:50 in humans, it is commonplace to approximate the sex-specific inbreeding sizes by $½N_{ef}$ such that the expected coalesce time for mt- and Y-DNA is N_{ef}. Coalescence theory also indicates that there can be a large amount of variation around these expected values.

The complete historical pattern of coalescent events that reduces the n copies of DNA sampled in the present to a single ancestral DNA molecule defines a gene tree. Recombination can greatly complicate the evolutionary history of a gene (Templeton et al., 2000), but fortunately much of the human genome, including all of the mtDNA, has little to no recombination. It is in such regions of no to little recombination that the evolutionary history of DNA is written most clearly. Another complication to reconstructing the gene tree is that when current copies of DNA are identical in sequence, there is no way to order their coalescent events historically. However, one or more mutations occurring in a DNA lineage provides the necessary genetic markers to observe past coalescent events among DNA lineages. The n copies of sampled DNA are sorted into haplotypes; that is, a genetically distinct set of nucleotide states over all variable sites in the DNA region being sampled. Standard phylogenetic techniques can then be used to estimate a haplotype tree that depicts the evolutionary relationships among the haplotypes as marked by mutational events. The haplotype tree is a lower resolution version of the gene tree, with the limit of resolution dependent on the number of mutations that have occurred since the ultimate coalescent event to the ancestral DNA molecule. It turns out that mtDNA has an exceptionally high mutation rate in humans, making it an ideal candidate for producing high-resolution haplotype trees.

Much was made of the fact that all human mtDNA coalesces back to a single ancestral molecule born by a single female individual (given that mtDNA is maternally inherited) (Cann et al., 1987). Indeed, this inference captured the public imagination, and the female bearing the ancestral mtDNA of all of humanity was soon called "mitochondrial Eve" in both general public and scientific articles, thereby linking mitochondrial coalescence to the Biblical story of the mother of us all. However, the equations for coalescence time given above are applicable to *all* samples of homologous DNA in *all* organisms—coalescence of a sample of homologous genes is a universal phenomenon. Thus, the coalescence of all human mtDNA to a common ancestral molecule borne by a woman is of no special significance per se, and is completely uninformative about models of human evolution. Moreover, mitochondrial Eve was not the mother of us all, only the ancestor for one small element of our total genetic legacy.

More informative was the inference that the root of the mtDNA haplotype tree was located in Sub-Saharan Africa between 140,000 and 290,000 years ago (Cann et al., 1987). This inference was regarded as strongly supporting the OAR model and falsifying the multiregional model. This was done by regarding mitochondrial Eve as a member of a distinct African population that was ancestral to all modern humans with no genetic input from any outside populations. This interpretation of mitochondrial Eve is unjustifiable by coalescent theory or population genetics. First, a single individual does not define a population. Did

the population in which mitochondrial Eve live have sharply defined genetic boundaries, or was her local population just a point on a continuum of genetic differentiation over a continuously distributed metapopulation? These and other questions simply cannot be answered from the inference of a single individual being the ancestral carrier of all modern mtDNA. Unfortunately, this scientifically indefensible elevation of a single individual to population status continues even in the recent literature on human evolution, as will be pointed out in the section dealing with ancient DNA. Second, because of gene flow, admixture, recombination, and assortment of chromosomes, coalescent theory does not predict that the ancestral individual for a particular piece of DNA, such as mtDNA, was a member of a population that was ancestral for all modern DNA. Subsequent studies clearly show that different components of the human genome coalesce to a common ancestral DNA sequence in different places (both Africa and Eurasia) and across millions of years of time (Templeton, 2007). This pattern vindicates Dobzhansky's insight that modern humans arose genetically from many different places and times and not a single population (Dobzhansky, 1944).

Hypothesis Compatibility Versus Hypothesis Testing

The original genetic evidence in favor of the OAR model was that there is a female ancestor of all modern mtDNA (mitochondrial Eve) who lived in Africa between 140,000 and 290,000 years ago (Cann et al., 1987). All of these inferences are indeed compatible with the OAR hypothesis, but they are also compatible with other models of human evolution. As noted earlier in this chapter, the existence of a mitochondrial Eve is a universal consequence of coalescence that is true under all models of human evolution. Under the multiregional model, the coalescence to a common mtDNA ancestral molecule could occur anywhere hominins were living, proportional to their regional population size. Since most hominins lived in Africa at that time (Relethford, 1998), Africa is the most likely place for this coalescent event under the multiregional model. Finally, as Dobzhansky (1944) so clearly pointed out, the DNA descendants of this ancestral mtDNA could spread throughout the world via gene flow or admixture long after the original expansion of *H. erectus* to Eurasia, so the date of coalescence between 140,000 and 290,000 years ago is also compatible with the multiregional model. The mtDNA coalescence time is also compatible with the mostly out-of-Africa model and the model shown in Fig. 5.2. The support for the OAR model could therefore also be regarded as support for many models of human evolution, but the data were generally presented as supporting only the replacement model. Indeed, throughout the debate about these models of human evolution, there was a strong tendency to avoid the scientific approach of hypothesis testing in favor of the weaker inference of hypothesis compatibility (Templeton, 1994). Again and again, proponents of the replacement model would search out for data compatible with their favored model, but not address the issue of whether or not these data actually tested the model in the sense of falsifying the alternatives. In this way, much data were assembled that gave the appearance of strong genetic support for the OAR model, but in reality none of these genetic data sets falsified most alternative models (Templeton, 1994, 2007).

There were some data sets that could be used to falsify some of the models of human evolution, including the original mtDNA data set of Cann et al. (1987). Cann et al. pointed out that a coalescence time between 140,000 and 290,000 years ago was incompatible with the candelabra model (Fig. 5.1C) as that model predicts that the common ancestral mtDNA of all living humans must have lived nearly 2 Ma (regarded as 1 Ma at the time of publication in 1987). Unfortunately, Cann et al. (1987) called the candelabra model (Fig. 5.1C) the "multiregional model" (Fig. 5.1B) even though these two models are diametrical opposites (Templeton, 2007). This misrepresentation was understandable given the long-established tendency in the anthropology literature to call both models multiregional. Indeed, one of the main goals of Dobzhansky's 1944 paper was to clarify the profound differences between these two models. Shortly after the publication of Cann et al. (1987), supporters of the multiregional model pointed out this misrepresentation (Wolpoff et al., 1988). Nevertheless, this misrepresentation continued, as did the effort to correct the misrepresentation (Wolpoff and Thorne, 1991; Wolpoff et al., 1994, 2000; Wolpoff, 1996). After repeated corrections, the proponents of the OAR model began to present the "multiregional model" as a candelabra model with a few arrows interconnecting the three major lineages to depict weak gene flow between them (Fig. 5.3). However, unlike the original multiregional model that had no separate lineages of humans but only locally differentiated populations in a geographical continuum due to gene flow (Fig. 5.1B), Fig. 5.3 portrays humanity as split into three major evolutionary lineages after *H. erectus* expanded out of Africa connected by only very limited genetic interchange. To avoid confusion with Weidenreich's no-lineage model, the model in Fig. 5.3 will be called the multiregional lineage model. However, even a weak gene flow model cannot be falsified by a coalescent date of mtDNA between 140,000 and 290,000 years ago, so now there was no genetic support in favor of rejecting even this multiregional model.

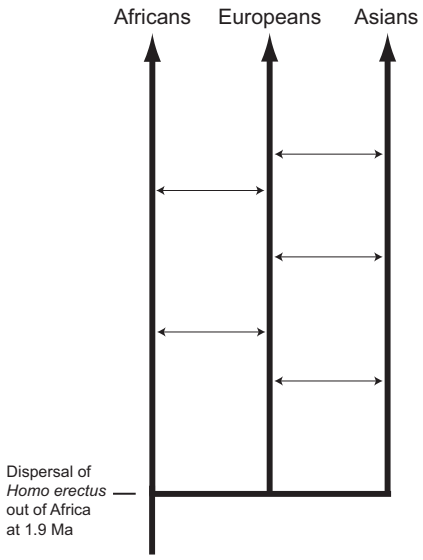

FIGURE 5.3 The multiregional lineage model of human evolution. Humanity is subdivided into three major lineages, shown by thick arrows, as under the candelabra model (Fig. 5.1C). However, the three lineages are now interconnected by weak and sporadic gene flow, shown by thin double-headed arrows between lineages.

There is one strong prediction of the replacement model that is testable with the same type of logic used by Cann et al. (1987) to falsify the candelabra model. Under the replacement model, all genome elements of modern humans are hypothesized to stem from a Sub-Saharan population that expanded out of Africa no earlier than 130,000 years ago, with no genetic input from archaic Eurasian populations. Hence, it is impossible under the replacement model for any DNA region in the human genome to coalesce to a Eurasian location at a time greater than 130,000 years ago but less than 1.9 Ma since those populations are hypothesized to have made no genetic contribution to modern humans. In contrast, under the multiregional model or multiregional lineage model, most genomic DNA regions should coalesce in Africa (where most hominins lived), but some could coalesce in Eurasia (Dobzhansky, 1944). The early phylogeographic studies (the geography of haplotype trees) almost always used mtDNA because this molecule was small and abundant, making it more amenable to study with the technology available at the time. Moreover, because mtDNA did not recombine, it was relatively easy to estimate haplotype trees. However, as DNA technology advanced and it was discovered that recombination in the nuclear human genome is concentrated into hotspots that separate areas of low to no recombination, it became increasingly common to study haplotype trees in the nuclear genome as well. Harding et al. (1997) reported haplotypes at the beta-hemoglobin locus that were of Asian origin and older than 200,000 years but much less than 1.9 Ma, and soon many other nuclear DNA regions were found to coalesce in Eurasia in this time range (Templeton, 2007). Each one of these old Eurasian coalescent events represents an absolute falsification of the OAR model. Hence, the genetic data clearly falsified the replacement model, but was compatible with the multiregional and multiregional lineage models, as well as the model shown in Fig. 5.2.

Although the proponents of the out-of-Africa replacement model readily embraced the falsification of the candelabra model on the basis of time to coalescence in Africa of mtDNA that was too recent for that model, the multiple observations of times to coalescence in Eurasia that falsified replacement had little to no impact on the dominance of the OAR model among much of the scientific community. Indeed, even when proponents of the replacement model discovered old Eurasian coalescent events themselves, they ignored the logical implications of this discovery and continued their support for African replacement. For example, Takahata et al. (2001) examined 15 X-linked and autosomal DNA regions and inferred the geographical root for 10 of these, with 9 being in Africa and 1 in Asia. Thus, the results reported in this paper patently falsified the OAR model (which they called "uniregionality") and indicated that roughly 10% of the nuclear genome of living humans was of non-African origin. However, they still supported "uniregionality" by claiming (Takahata et al., 2001, p. 174), "However, emphasizing the overwhelming genetic contribution of only one founding population is equivalent to uniregionality." Thus, Takahata et al. (2001) dismissed the falsification of the replacement model by their own analysis by redefining the OAR model to be "equivalent" to the mostly out-of-Africa model. However, as pointed out long ago by Dobzhansky (1944), a model that has most but not all of modern human genetic ancestry coming from one region is actually a special case of the multiregional model because it incorporates the evolutionary forces of gene flow and/or admixture and results in a mixed genetic ancestry for modern humans across space and time.

Some types of computer simulation were also used to access hypothesis compatibility without hypothesis testing. This approach is illustrated by two papers that came out within a week of each other, but with opposite conclusions. Eswaran et al. (2005) simulated the OAR model and an isolation by distance model extending over Africa and Eurasia with some selective sweeps, in accordance with the multiregional model. They concluded that the isolation by distance model with selection explains well the observed patterns of genetic distances and diversities, whereas the replacement model does not. Indeed, the title of their paper was "Genomics refutes an exclusively African origin of humans." About one week later, Ray et al. (2005) simulated the OAR model and the "multiregional" model (actually,

the multiregional lineage model; see Fig. 5.3). They claimed that their simulations strongly favored the OAR model over the multiregional lineage model. One way of resolving these apparently contradictory results is to notice that both simulations are consistent with the ordering: multiregional with isolation by distance > OAR > multiregional lineage with weak gene flow. That is, although both papers simulated a multiregional model, they were not the same multiregional model. Hence, there is no necessary contradiction between these two sets of simulations. However, a more fundamental problem is that neither paper presents any formal tests of alternative hypotheses. Instead, both papers give a heuristic assessment of goodness of fit of the data to the simulated models but with no evaluation of whether the goodness of fit measures among the various models are significantly different or not. Thus, both papers merely show hypothesis compatibility with a favored scenario with no hypothesis testing.

Computer Simulations With Bayesian Hypothesis Testing

One method of combining hypothesis testing with computer simulation is through the method of approximate Bayesian computation (ABC). In ABC, a detailed model or models of the evolutionary history of a group of interest is constructed. Such detailed models often depend upon many parameters whose values are not known. A prior probability distribution is assigned to these parameters, and the evolutionary scenarios are simulated many times, drawing parameter values from the prior distributions. Various summary statistics are calculated at the end of each simulation that are chosen to be informative about the models to be tested, and the results of repeated simulations can be used to approximate the posterior probabilities on the parameters and summary statistics. These posterior probabilities can then be used in a variety of ways, both to estimate parameters and to test hypotheses.

Fagundes et al. (2007) purported to provide statistical evidence in favor of the OAR model. They simulated three basic types of models of human evolution: the replacement model (Fig. 5.1A); a model identical to Fig. 5.1A except it allowed for admixture of the expanding African population with Eurasian populations by adding an admixture parameter M to the OAR model that can vary from 0 (no admixture) to 1 (complete admixture); and the multiregional lineage model (Fig. 5.3). The resulting posterior probabilities on these three models were 0.781 for the replacement model, 0.001 for the model allowing admixture, and 0.218 for the multiregional lineage model. There are two important features of these probabilities. First, their ABC simulations did not discriminate between the OAR model and the multiregional lineage model with weak gene flow. The probability of 0.218 for the model with gene flow is not regarded as low enough to reject a model in the general scientific literature. Commonly, a threshold of 0.05 or smaller is required. The probability of 0.001 for the model with admixture seemingly would reject the hypothesis of any admixture of the expanding African population with Eurasian populations, but there is a fundamental problem with this probability. Fagundes et al. (2007) explicitly treated these three models as mutually exclusive alternatives, but the replacement model is actually a special case of their admixture model that occurs when $M = 0$; that is, the replacement model is logically nested within their admixture model. One of the fundamental properties of probability measures is that the probability of an event nested within a more general event must be less than or equal to the probability of the general event. Obviously, 0.781 is not less than or equal to 0.001—a mathematically impossible result for a probability measure. Such a violation of elementary probability theory and Boolean logic is called incoherence, so their rejection of admixture is an incoherent inference (Templeton, 2010) that was a mathematical artifact of erroneously treating a nested model as if it were an exclusive model. By using the *same* posterior probabilities generated by these simulations with a well-established coherent Bayesian test, the null hypothesis of no admixture ($M = 0$; that is, the OAR model) was *rejected* relative to the more general admixture model with a probability less than 0.025 (Templeton, 2010)—a reversal of the relative probabilities of these two models by five orders of magnitude! It is important to note that this reversal is not a flaw of the ABC method per se because the reversal is based on the *same* ABC posterior probabilities; rather, it reflects a serious statistical and logical flaw in how Fagundes et al. (2007) used their priors before the simulations were performed and the posterior probabilities after the simulations. Hence, contrary to the claims of Fagundes et al. (2007), the ABC approach when used in a coherent fashion rejects replacement in favor of limited admixture of the expanding African population with populations in Eurasia. This result is compatible with the falsification of replacement by Eurasian coalescent events in haplotype trees, that also indicated limited admixture (Templeton, 2007).

Building Models Through Hypothesis Testing

The early phylogeographic studies in both humans and other species were mostly based on overlaying a haplotype tree (usually a mtDNA tree) upon geography and describing a scenario compatible with that overlay. This was strictly an exercise in hypothesis compatibility. There

was no hypothesis testing, and there was not even any testing to see if the sample sizes were large enough to result in a haplotype tree that had significant geographic associations. Nested clade phylogeographic analysis (NCPA) was developed to address these deficiencies (Templeton, 1998b; Templeton et al., 1995), thereby initiating the field of statistical phylogeography. Once a haplotype tree has been estimated [allowing uncertainty, which is quantified using a Bayesian procedure (Templeton and Sing, 1993)], the association of the haplotype tree with geography is quantified by distances that measure the geographical extent of a haplotype and of clades (a branch in the haplotype tree) and the geographical distances between haplotypes and clades that are evolutionarily close together on the haplotype tree. A statistical test is then performed to identify those distances that are significantly large or small. If none of the distances are significant, there is no significant association of the haplotype tree with geography. If there are significant geographical associations, these significant associations are interpreted using coalescent theory to make phylogeographic inferences. The validity of this inference structure was tested against many known cases of phylogeographic events, making NCPA the most validated method of phylogeographic inference (Templeton, 2008, 2009b).

The original NCPA was a single-DNA region analysis, reflecting the empirical fact that almost all phylogeographic studies at the time were based only on mtDNA. As DNA technology advanced, it became possible to include nuclear DNA regions. One major limitation of NCPA is that it requires a haplotype tree of the DNA region, which in turn requires a DNA region with little or no recombination. Fortunately, the human genome has recombination concentrated into hotspots separated by stretches of no or little recombination. The low recombination stretches are regions at which evolutionary history is most clearly written and are the most informative about past human evolutionary events. Accordingly, a multilocus version of NCPA was developed (MLNCPA) (Templeton, 2002). A cross-validation and expanded hypothesis testing framework was developed (Templeton, 2002, 2004a,b, 2009a) allowing direct statistical testing of all phylogeographic hypotheses. The strength and validity of MLNCPA was confirmed by computer simulations. Knowles and Maddison (2002) simulated a difficult phylogeographic scenario of microvicariance. The phylogeographic approaches that they favored did not perform well with these simulations, but neither did NCPA. However, they used the single-locus, 1998 version of NCPA despite the fact that MLNCPA had been published nine months earlier. Moreover, the single-locus NCPA inference structure explicitly excludes microvicariance (Templeton et al., 1995), so the poor performance of single-locus NCPA was not surprising. However, when the 2002 version of MLNCPA was applied to the simulation outputs of Knowles and Maddison (2002), a 100% accurate phylogeographic reconstruction was possible without any false positives or false negatives (Templeton, 2009b), thereby illustrating the ability to make accurate inference in the most difficult of phylogeographic situations that was impossible with single locus analyses. Panchal and Beaumont (2010) directly tested MLNCPA using computer simulations of a variety of phylogeographic situations, and concluded that there was a high false positive rate. However, this conclusion was due exclusively to their treatment of gene flow. Panchal and Beaumont (2010) claimed that there was no statistical test for concordance of gene flow inferences, so they performed no tests and obtained a high error rate *only* for gene flow inferences. However, these tests do exist and were given in the papers that Panchal and Beaumont (2010) cited as their sources for how to implement MLNCPA (Eq. 12 in Templeton, 2004a; Eq. 2 in Templeton, 2009a). Once this patently false claim of Panchal and Beaumont (2010) is corrected, the actual false positive error rate in their simulations is always below the nominal rate of 5% (Templeton, 2013, 2015). Hence, the computer simulations of Panchal and Beaumont (2010) strongly vindicate the statistical validity of MLNCPA.

Fig. 5.2 shows all the statistically significant inferences arising from an MLNCPA of 25 regions of human genomes with little to no recombination (for details, see Templeton, 2004a, 2009a, 2015). Although some have presented MLNCPA and ABC phylogeographic analysis as antagonistic opposites (Beaumont and Panchal, 2008), in reality they are highly synergistic techniques that complement one another (Templeton, 2015). One great strength of MLNCPA over ABC is that MLNCPA does not require a prior model; rather, the model, such as that shown in Fig. 5.2, emerges naturally through statistical hypothesis testing. In contrast, a detailed model(s) has to be specified a priori with ABC, and all inference is limited to just the models simulated. Because no prior model is needed, MLNCPA can discover unanticipated features of human evolution not found in any of the prior-model approaches. For example, MLNCPA discovered a significant range expansion out of Africa into Eurasia during the mid-Pleistocene that occurred at a significantly different time than the expansion of *H. erectus* out of Africa and that of anatomically modern humans out of Africa, indicating that there were at least three out-of-Africa expansions, not two (Fig. 5.2). This middle expansion is consistent with the archaeological and paleontological record that indicates a major cultural transition, the Acheulean, that first arose in Africa in the Early Pleistocene and then spread into Eurasia during the mid-Pleistocene during a favorable climatic regime (Alperson-Afil et al., 2009; Cuenca-Bescós et al., 2011; Pei et al., 2015; Potts et al., 2004; Rightmire, 2009; Scott and Gibert, 2009), although there may have been a

more limited expansion in the Early Pleistocene into India (Pappu et al., 2011) not detected by MLNCPA. Moreover, the null hypothesis that the Acheulean expansion was a replacement event is rejected at the 5% level of significance ($p = 0.003$) in favor of admixture of the Acheulean population with Eurasian hominin populations. Despite all this genetic, archeological, paleontological, and paleoclimatic evidence favoring a mid-Pleistocene expansion out of Africa, this expansion was totally ignored in the simulations of Fagundes et al. (2007) even though most of this evidence was available before 2007. In terms of the Bayesian framework used in their paper, they assumed a prior probability of zero (absolute certainty) that an Acheulean expansion never occurred, without a single citation explaining their certainty and their rejection of the prior genetic, archeological, and fossil evidence for the Acheulean expansion. Bayesian approaches have and continue to be controversial because, as pointed out by the statistician B. Efron (2013), "The trouble and the subsequent busts [of Bayesian approaches] came from overenthusiastic application of the theorem in the absence of genuine prior information." Efron therefore recommends "to use Bayesian analysis in the presence of genuine prior information." In this case, much genuine prior information did exist, and the prior probability invoked by Fagundes et al. (2007) was *incompatible* with all prior information. This is indefensible within a Bayesian framework.

Many of the other features portrayed in the MLNCPA model in Fig. 5.2 represent a mixture of features found in the prior models described earlier. After the expansion of *H. erectus* out of Africa at 1.9 Ma, there is no statistically significant evidence for gene flow between the African and Eurasian populations, consistent with the candelabra model. After the Acheulean expansion, the null hypothesis of no gene flow between African and Eurasian populations is rejected in favor of a hypothesis of gene flow restricted by isolation by distance in which individuals or groups mostly interbred with nearby populations but with no permanent barriers to gene flow within the range of the species, as under the multiregional model. This recurrent gene flow after the Acheulean expansion (perhaps only recurrent on a time scale of tens of thousands of years as the resolution of MLNCPA is coarse) is consistent with frequent "green Sahara" periods after the mid-Pleistocene until about 80,000 years ago, when the Sahara entered into its most consistent desert-like phase in the past 350,000 years (Larrasoña, 2012). Around 130,000 years ago, anatomically modern humans expanded into Eurasia out of Africa (Fig. 5.2), as under the OAR model, but the null hypothesis of no admixture (replacement) is strongly rejected with a statistical significance of 10^{-16}. However, the admixture was at a low level as under the mostly out-of-Africa model (Templeton, 2002). Recall that the ABC procedure also rejected the hypothesis of replacement in favor of admixture when analyzed coherently, but with a much weaker p-value of 0.025. Part of this weaker rejection of replacement stems from the priors used by Fagundes et al. (2007). As already noted, they used a prior probability of zero for the Acheluean expansion in spite of diverse prior information to the contrary. They also had a prior probability of zero (absolute certainty) for no gene flow at all between Africa and Eurasia throughout the Pleistocene despite the previously published MLNCPA results that indicated such gene flow. Finally, they placed prior probabilities on the size of the Eurasian population that was several fold too small given the prior publication of nuclear DNA coalescence times that are directly proportional to inbreeding effective sizes, as pointed out earlier. The impact of all these "priors" that were incompatible with the prior information available at the time was to strongly bias their simulation results against admixture and in favor of replacement (Templeton, 2010). Despite this strong bias, the resulting posterior probabilities still rejected replacement and favored a mostly out-of-Africa model when analyzed in a statically coherent fashion.

MLNCPA makes it clear that some aspects of all the prior-models of human evolution are defensible within a hypothesis-testing framework, but none of the prior-models has all of its elements justified via hypothesis testing. Moreover, all of the prior models of human evolution missed important features, such as the Acheulean expansion.

Ancient DNA Studies

All of the genetic studies described up to now used samples of living peoples to make inferences about the past. As DNA technology has advanced, it has become possible to look directly at DNA from human fossils, thereby providing a direct window into our evolutionary past.

The oldest hominin ancient DNA is mtDNA from a fossil in Northern Spain that is over 300,000 years old (Meyer et al., 2014), and perhaps 400,000 years old (Orlando, 2014). The skeletal remains display distinct Neandertal features and other traits associated with its European location, but the mtDNA is closely related to mtDNA genomes from Eastern Eurasia. This indicates that archaic human populations across the Eurasian continent were not genetically isolated. Ancient DNA from a 24,000-year-old fossil indicates that this pattern of genetic interconnectedness across large distances continued such that a single metapopulation stretched from Europe to Asia in the Upper Paleolithic (Seguin-Orlando et al., 2014). These results support the inference from MLNCPA that gene flow, although restricted by isolation by distance, has existed since the mid-Pleistocene and continues to the present.

By far the most controversial inference from MLNCPA was the strong rejection of replacement in favor of limited admixture, about 10%. This inference has been strongly vindicated by ancient DNA studies. DNA has been isolated and sequenced from Neandertal fossils (Green et al., 2010), a population of archaic humans that lived in the western half of Eurasia and that coexisted with anatomically modern humans after their expansion out of Africa, thereby providing the opportunity for gene flow or admixture. The ancient DNA studies on Neandertals clearly show that genetic interchange with modern humans occurred with an admixture rate of 3.4−7.3% (Lohse and Frantz, 2014). DNA was extracted from another archaic individual found in Denisova Cave in Southern Siberia (Meyer et al., 2012), and some 4−6% of the DNA found in modern Melanesians traces to DNA from the Denisovan specimen (Reich et al., 2010), with other modern Asian and Indonesian populations showing evidence of some genetic introgression as well (Mendez et al., 2012; Povysil and Hochreiter, 2014). Hence, as inferred originally through MLNCPA hypothesis testing, replacement has been falsified in favor of limited admixture.

The original depiction of the ancient DNA studies was as if two isolated events of admixture occurred that allowed introgression of archaic hominin genes into modern populations (Reich et al., 2010). However, with more data and analysis, this picture has proven to be too simple. The ancient DNA is sparse in time and space and with limited sample sizes, and this makes it difficult to distinguish between an admixture event versus recurrent genetic interchange, including isolation by distance (Eriksson and Manica, 2014). With additional sampling from modern populations, it became evident that Neandertals contributed more to East Asian populations than to Europeans, and that Neandertal and Denisovan DNA is also found in Sub-Saharan African populations (Povysil and Hochreiter, 2014; Wall et al., 2013), indicating a broad spread of these archaic genes throughout modern humanity. Additional ancient DNA sequences indicated that several gene flow events occurred among Neandertals, Denisovan-related individuals, and early modern humans (Prufer et al., 2014). Indeed, it is now apparent from ancient DNA studies that our ancestors were part of a web of "populations linked by limited, but intermittent or sometimes perhaps even persistent, gene flow" (Paabo, 2015, p. 313), exactly as inferred from MLNCPA (Templeton, 2002, 2015).

Although the evidence indicates that multiple gene flow/admixture events occurred between modern humans and archaic Eurasian populations, the results clearly show that this was a mostly out-of-Africa model. Recall that Dobzhansky (1944) regarded such a model as a multiregional model rather than a replacement model. Dobzhansky, through his own work on fruit flies, was well aware that even limited genetic interchange can have dramatic evolutionary consequences, so that there is an important qualitative evolutionary difference between no gene flow or admixture (replacement) versus even small amounts of gene flow or admixture. Even limited genetic interchange can introduce genetic variation into a population's gene pool at a rate far greater than that possible through mutation, and genetic variation is the raw material of all evolutionary change. Long ago, Workman et al. (1963) demonstrated in modern human populations that admixture is a very dynamic and heterogeneous evolutionary force, with neutral genes introgressing at the gene flow/admixture rate, other genes being stopped from introgression by selection against them in their new gene background or environment, and yet other genes increasing rapidly in frequency due to positive selection once introduced by gene flow or admixture. The ancient DNA studies make it clear that the same was true when modern humans came out of Africa and began to interbred with Eurasian populations. Some Neandertal alleles have been selected against, perhaps due to decreased male fertility when placed on a modern human genetic background, whereas other Neandertal alleles have been selected for and have helped modern humans adapt to non-African environments (Racimo et al., 2015; Sankararaman et al., 2014), such as skin phenotypes (Vernot and Akey, 2014), response to ultraviolet radiation B (UVB) irradiation that varies with latitude (Ding et al., 2014), and high altitude adaptation (Huerta-Sanchez et al., 2014). Interestingly, modern humans and the archaic Eurasian populations shared most of the same alleles for cognitive genes (Paixão-Côrtes et al., 2013).

FOSSILS, ARCHAEOLOGY, AND MODELS OF HUMAN EVOLUTION

One Human Lineage or Multiple Species?

The human fossil record is more complete than that for many other taxa, but it is still sparse over both time and space with a few exceptions. This sparseness causes many difficulties in the interpretation of the hominin fossil record over the last 2 million years. The paleoanthropological literature varies from having just one hominin species at any given time during the Pleistocene to having multiple species coexisting until modern humans became dominant (Curnoe and Thorne, 2003; Hunt, 2003), with estimates as high as 27 archaic species (Bokma et al., 2012). Although this variety of opinion is often described as a debate between "lumpers" versus "splitters" (Bokma et al., 2012), a more accurate distinction is between essentialistic or typological thinking versus population thinking (Wolpoff and Caspari, 2000). Essentialism regards species as natural types that can be represented by a "type specimen," with individual variation from the type being nonessential or accidental (Mayr, 1994). In contrast,

population thinking regards individuals as uniquely different, with this individual variation being the critical biological feature of the species that allows evolution to occur, including the origin of the species itself (Mayr, 1994). With the acceptance of Darwinian evolution, population thinking should completely displace typological thinking in biology (Mayr, 1982), but typological thinking is still common in paleoanthropology and has played a critical role in the debate about models of human evolution (Wolpoff and Caspari, 2000). Typological thinking is well illustrated by the elevation of the Denisovan specimen to species status (Bokma et al., 2012). This "species" is defined by two teeth and a part of one finger at one site, and by ancient DNA studies on this one individual. From the most elementary principles of population genetics and statistics, such a sample is inadequate to make an inference of a "species" or even a distinct population or hominin lineage within a species. What are the boundaries of this species or population temporally and geographically? Indeed, is it a population at all in any meaningful sense, or is this an individual fossil and genome from a continuum of populations interconnected by gene flow without distinct population-level boundaries? Of course, one cannot answer these questions from a single specimen. Yet the literature generally refers to the Denisovans rather than the Denisovan specimen and portrays "them" as a distinct lineage or species of archaic hominins that "split" from the rest of humanity, complete with an estimated time of this ancient "population separation" (Reich et al., 2010).

The Denisovan specimen illustrates the fundamental problem of much of paleoanthropology: the fossil record is often so sparse in time and space that it is difficult to implement population thinking because there exists only one or very few specimens. Two methods have been used to overcome this extreme sparseness. First, one can use living species (typically modern humans, chimpanzees, gorillas, or baboons—the other primate species in addition to humans that adapted to a terrestrial, savanna environment) as models of intraspecific variation and test the null hypothesis that the variation found in fossil specimens, often at widely scattered sites and times, falls within these modern models of intraspecific variation (Ackermann, 2002; Ackermann and Smith, 2007; Thackeray, 2007; Thackeray et al., 1997). When this hypothesis-testing, population approach is applied to the human fossil record over the past 2 million years, the null hypothesis of a single species can rarely be rejected for roughly contemporaneous fossils even when they are pooled together from both Africa and Eurasia (Ackermann, 2002, 2005; Baab, 2008; Van Arsdale and Wolpoff, 2013; Villmoare, 2005). This is also true for "anatomically modern humans" versus contemporaneous "archaic humans," which are generally treated as distinct, well-defined groups in much of the human evolution literature. In reality, the morphology of these groups is highly variable in the fossil record (including being highly variable in living humans), with different "modern" traits displaying disparate geographical and temporal patterns, resulting in indistinct borders between "archaic" and "modern" fossil specimens (Pearson, 2008). Treating "anatomically modern humans" and "archaic humans" as separate species reinforced the idea of replacement rather than admixture, as a new "species" came out of Africa and displaced a more primitive, separate "species." With population thinking, this scenario turns into a differentiated but variable human population coming out of Africa that encountered other human populations of the same species in Eurasia. This later scenario makes genetic interchange seem much more reasonable, and as shown in the previous section, that is what the genetic data indicate.

The second way of addressing the problem of the sparseness of the fossil record is to make use of the few exceptions: that is, sites that yield large numbers of individual specimens found in a narrow time range. Such sites allow a direct implementation of population thinking. For example, the Dmanisi site in Georgia provides the earliest evidence for *H. erectus* outside of Africa, dating to 1.85 to 1.78 Ma (Ferring et al., 2011). This site has produced crania from five individuals over a time range of centuries—a small sample for living populations, but large for a human fossil site this old. These five skulls span a large morphological range and encompass the range of variation previously used to define three separate contemporaneous species of *Homo* from Africa and Eurasia (Lordkipanidze et al., 2013). Productive sites from the Middle and Late Pleistocene reveal a similar pattern, with extreme variability within a site coupled with remarkable similarity between sites that are roughly contemporaneous. These discoveries at the handful of rich fossil sites imply "sporadic, but continuing multi-directional migrations and gene flow" (Simmons, 1999, p. 107).

In light of these two lines of evidence and a preference for hypothesis testing and population thinking, there are no convincing fossil data to reject the null hypothesis of a single hominin species at any given time throughout the entire Pleistocene. Different species only exist in the sense of chronospecies; that is, the evolution over time of a named species into a differently named species because of the accumulation of many evolutionary changes over time. There certainly could have been isolated populations throughout this period, but there is no evidence subject to a hypothesis testing framework to suggest that any such isolated population speciated into a novel hominin species that coexisted at the same time with other hominin species.

Concordance of Fossils and Archaeology With Models of Human Evolution

The failure to reject the null hypothesis of only a single hominin species throughout the Pleistocene is difficult to reconcile with the OAR model (Fig. 5.1A) or the candelabra model (Fig. 5.1C), as both of these models have human populations isolated from one another for over 1.7 million years. However, a single hominin species is compatible with the original multiregional model (Fig. 5.1B), the multiregional model with weak gene flow (Fig. 5.3), or the model that emerges from MLNCPA (Fig. 5.2).

The MLNCPA analysis (Fig. 5.2) is remarkably concordant with the fossil, archaeological, and paleoclimatic data in many of its details (Templeton, 2015). Its first statistically significant inference is an expansion out of Africa into Eurasia that dates to 1.9 Ma just using the genetic data alone. This is consistent with the fossil record that finds *H. erectus* fossils exclusively in Africa until 1.85 to 1.78 Ma when they first appear in Eurasia (Ferring et al., 2011). Next, there is a limited period of potential isolation that certainly ends in the mid-Pleistocene with the Acheulean expansion and its resulting admixture. As discussed earlier, the Acheulean expansion is also supported by the fossil, archaeological, and paleoclimatic records. The establishment of statistically significant levels of gene flow restricted by isolation by distance by the mid-Pleistocene is consistent with the fossil pattern of much variation within sites with little differentiation between sites found in this time period (Simmons, 1999) and with the recurrent green Sahara paleoclimatic phases in this time period (Larrasoña, 2012). The next statistically significant inference from MLNCPA is an expansion with admixture of modern humans out of Sub-Sahara Africa dated at 130,000 years ago with the genetic data (Fig. 5.2). This date is consistent with this being an expansion of anatomically modern humans as the fossil record shows that many anatomically modern traits first appeared in Sub-Saharan Africa around 200,000 years ago (McDougall et al., 2005). However, the date of 130,000 for the out-of-Africa expansion was another source of controversy about the model emerging from MLNCPA because most of the advocates of the OAR model dated this expansion to about 60,000 to 70,000 years ago (eg, Fagundes et al., 2007). The fossil and archeological records support the older date suggested by MLNCPA, indicating that anatomically modern humans appeared outside of Sub-Saharan Africa in Northern Africa, the Arabian Peninsula, and the Levant between 130,000 and 125,000 years ago (Armitage et al., 2011; Grun et al., 2005; Vanhaeren et al., 2006). This evidence has been dismissed by advocates of the more recent out-of-Africa expansion as a temporary excursion of anatomically modern humans into this region that is close to Sub-Saharan Africa but that did not expand into the rest of Eurasia (Soares et al., 2012). However, this explanation is inconsistent with the archeological record that indicates modern humans were in India by at least 74,000 years ago (Haslam et al., 2011) and by the discovery of modern human fossils in far eastern Asia at least by 110,000 years ago (Jin et al., 2009; Liu et al., 2010). Hence, the fossil and archeological records indicate that the expansion of anatomically modern humans began at 130,000 years ago and had reached the eastern part of the Eurasian continent by 110,000 years ago or earlier—a result consistent with MLNCPA. The MLNCPA dating has also been supported by more recent genetic analyses. After recalibrating the molecular clock by direct estimates of human mutation rates using next-generation sequencing, Scally and Durbin (2012) dated the origin of non-African modern humans to 90,000 to 130,000 years ago, and an analyses of Y-DNA dated this origin to 115,000 years ago (Scozzari et al., 2014). A genetic and cranial morphological analysis (Reyes-Centeno et al., 2014) also supports the older date of 130,000 years ago, as well as the inference from MLNCPA (Fig. 5.2) that the out-of-Africa expansion of modern humans was a two-stage process, with the initial expansion being primarily along the southern part of Eurasia followed by an expansion into Northern Eurasia around 50,000 years ago.

IMPLICATIONS OF RECENT HUMAN EVOLUTION FOR CURRENT PATTERNS OF HUMAN GENETIC DIVERSITY

The Impact of Gene Flow and Admixture on Genetic Diversity

By taking a strict hypothesis testing approach, all models of human evolution that do not incorporate gene flow and admixture since at least the mid-Pleistocene can be rejected. Repeated episodes of admixture overlaid upon recurrent gene flow since the mid-Pleistocene have resulted in humans evolving into their current state as a single evolutionary lineage with most genetic diversity found among individuals within populations and modest levels of genetic differentiation among populations, even those on different continents (Templeton, 2013). Indeed, humans are one of the most genetically homogeneous species across space despite our global geographical range (Templeton, 1998a).

There is still some genetic differentiation among human populations. Most of the gene flow inferred in recent human evolution has been restricted by isolation by distance, with some long distance gene flow (Fig. 5.2). Isolation by distance does lead to genetic differentiation among populations, particularly those that are located far apart from

each other, but this level of genetic differentiation is still modest in humans, even between geographically distant populations (Templeton, 2013). Another aspect of the impact of isolation by distance upon the distribution of human genetic diversity is that the genetic differences between human populations accumulate gradually with distance, with no obvious breaks once one adjusts for the fact that until recently, most human movements were over land and avoided long distances over water (Fig. 5.4, based on a figure from Ramachandran et al., 2005). Gene flow and admixture obviously play a major role in determining how genetic diversity is distributed within and between human populations.

Much stronger genetic differentiation is possible between human populations for specific alleles favored by natural selection to local environmental conditions. For example, human populations living in malarial regions have high frequencies of alleles that confer resistance to malaria, such as the sickle-cell allele that is in high frequency in the malarial regions of Africa, the Arabian Peninsula, and India. The sickle-cell allele is in low frequency in human populations living in nearby areas that do not have malaria (Templeton, 2006). When local environments change gradually over space, human adaptations to those environments often result in gradual clines. For example, skin color is an adaptation to the level of UVB in the environment, representing a balance between natural selection favoring dark skin to protect the individual from the damage that UVB can induce versus natural selection favoring light skin to allow the production of vitamin D (Hochberg and Templeton, 2010; Jablonski and Chaplin, 2013). UVB is most intense in the tropics and falls off with increasing latitude away from the tropics. Human skin color shows gradual clinal variation that tracks these latitudinal differences, with darker skin in the tropics versus lighter skin in the higher latitudes (Jablonski and Chaplin, 2013).

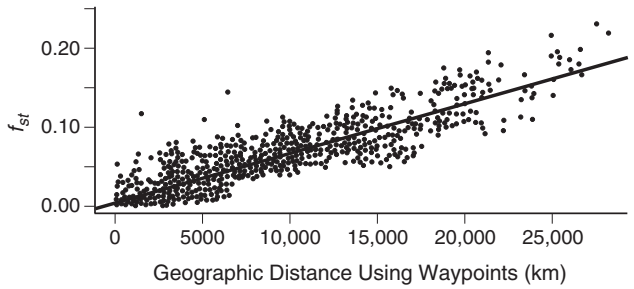

FIGURE 5.4 Isolation-by-distance in human populations. The *x*-axis is the geographical distance between two populations, as measured through waypoints that minimize travel over oceans. The *y*-axis is the pairwise f_{st} between two populations, a standard measure of genetic distance. *Modified from Ramachandran, S., Deshpande, O., Roseman, C.C., et al., 2005. Support from the relationship of genetic and geographic distance in human populations for a serial founder effect originating in Africa. PNAS 102, 15942–15947.*

To Tree or Not to Tree, That Is the Question

It is commonplace in the human evolutionary literature to portray human populations as long-standing evolutionary lineages that define branches on an evolutionary tree of human populations (eg, see Figs. 5.1A,C and 5.3). Population trees occur when populations "split" from one another, followed by long-term isolation with no or very weak gene flow with other "branches." Many computer programs exist that will construct such trees, often estimating the times of the splits as well. However, these programs will construct such trees from any genetic data set regardless of whether or not the underlying genetic data are actually compatible with a tree-like structure of population splits and isolation. Hence, Smouse (1998) wrote a paper entitled "To tree or not to tree, that is the question." His answer was simple: when dealing with intraspecific samples, populations generally define a multiply interconnected network due to gene flow and admixture rather than a strict evolutionary tree (Smouse, 1998, 2000). Why, then, do population trees dominate the human evolutionary literature and not network diagrams?

The frequent presentation of human population trees is certainly not because of hypothesis testing. One of the earliest measures of how well a genetic data set fit the constraints of a tree-like structure was the cophenetic correlation. This correlation measures the fit between the observed genetic distances between populations with the expected genetic distances assuming an optimized tree (Rohlf, 1993). Many human data sets were scored with this measure, all of which had come from publications that presented population trees based on these data, but not a single data set fit the constraints of an evolutionary tree with this measure (Templeton, 1998a). A statistical test of the null hypothesis of a population tree was presented by Cavalli-Sforza and Piazza (1975). Long and Kittles (2003) updated this test and applied it to genetic data drawn from global human populations. The test of the null hypothesis of a strict population tree was rejected with a p-level of 3.8×10^{-49}. The fit to a relaxed tree that allowed different rates of genetic divergence on each branch was also rejected with a p-level of 1.3×10^{-9}. Hence, there is an overwhelming rejection of the null hypothesis that human populations fit a population tree of splits and isolation. A population tree is also impossible to reconcile with the genetic distance data shown in Fig. 5.4. If a human

population tree did exist, there would be strong breaks and a step-like appearance to genetic distance versus geographical distance plots (Templeton, 2013). Fig. 5.4 shows that this is not the case.

Do Human Races Exist?

Human races certainly exist in a cultural, social, economic, and political sense, but are they biologically meaningful categories? Races, or subspecies, are geographically circumscribed populations within a species that have sharp genetic boundaries that separate them from the remainder of the species (Templeton, 2013). The boundary can be defined either quantitatively as exceeding some threshold level of genetic differentiation, or qualitatively as arising from separate evolutionary lineages or branches of a population tree within the species (Templeton, 2013). The concept of race is inapplicable to humans because there are no sharp genetic boundaries of any sort in humans, as shown in Fig. 5.4 for neutral genetic variation. Adaptive traits, such as skin color that is also used to define races culturally, mostly show clinal variation and not sharp boundaries. In some parts of the world, a history of colonization sometimes creates the appearance of sharp boundaries in skin color. For example, the colonization history of North America placed together three human populations from distant geographical locations (Native American, Western European, and Western, tropical African) with few individuals coming from geographically intermediate areas. These "sharp" boundaries are simply a historical artifact of colonization and do not reject the biological reality observed from more complete geographical sampling, such as that shown in Fig. 5.4. Another aspect of Fig. 5.4 is that even the maximum genetic distances observed between human populations at the global level are below the thresholds used in the nonhuman literature to identify subspecies (Templeton, 2013). As noted in the section on population trees, the hypothesis that humans are subdivided into distinct, mostly isolated branches is overwhelmingly falsified when put into a hypothesis-testing framework.

MLNCPA can also be used to test for separate evolutionary lineages in both positive and negative senses. Nested clade analysis is particularly powerful at detecting fragmentation events (splits followed by isolation, although weak levels of gene flow are not excluded) as shown both by the analysis of known fragmentation events (Templeton, 1998b, 2004b) and simulated fragmentation events (Templeton, 2009b). Yet, the null hypothesis of no fragmentation events in human evolutionary history over the last 2 million years cannot be rejected (Templeton, 2015). Because the temporal resolution of MLNCPA is coarse, isolated populations could have existed on the order of tens of thousands of years, but there is no evidence for longer periods of fragmentation in our species. Alternatively, MLNCPA can test the null hypothesis that the populations from a specific geographical area have been significantly isolated from other populations in the species over a specified time interval (Templeton, 2009a). Using this test, the null hypothesis of isolation between African and Eurasian populations cannot be rejected for the early Pleistocene, but the null hypothesis of isolation is rejected from the mid-Pleistocene to the present (Fig. 5.2). Combining the results of testing both of these null hypotheses, there have been no long-term human isolates since the mid-Pleistocene. Hence, there are no biological races in modern humans.

SUMMARY AND CONCLUSIONS

Hypothesis Testing in Scientific Inference

Testing hypotheses, and in particular the falsification of a hypothesis, is often regarded as one of the strongest types of scientific inference (Popper, 1959). Yet, after the publication of Cann et al. (1987), the OAR hypothesis dominated the human evolutionary genetic literature for almost a quarter of a century despite the fact that not a single genetic data set ever supported it within a hypothesis testing framework and several genetic data sets overwhelmingly rejected and falsified it, as shown throughout this article. Moreover, advocates of the replacement model did not attempt any statistical hypothesis testing of replacement versus other models with only one exception, the ABC analysis of Fagundes et al. (2007). Although this paper was presented as support for replacement, even a complete acceptance of their results does not support this conclusion as the posterior probability of replacement was 0.78 and that of the multiregional lineage model was 0.22. Using the norms for statistical inference, the only conclusion that is justified from their published analysis is that their data are compatible with both replacement and the multiregional lineage model. Moreover, the strong rejection of any model with nonzero admixture (a posterior probability of 0.001) was based on a failure to properly account for the logical relationships of the models being tested, resulting in a mathematically impossible, incoherent result. When this mistake was corrected by using a coherent statistic with the *same* posterior probabilities, the replacement model was rejected with a probability value of 0.025 for replacement compared to an admixture model (Templeton, 2010). Hence, by 2010, multiple genetic data sets and analyses had falsified or significantly rejected the replacement hypothesis, and not a single statistical test supported it. Yet

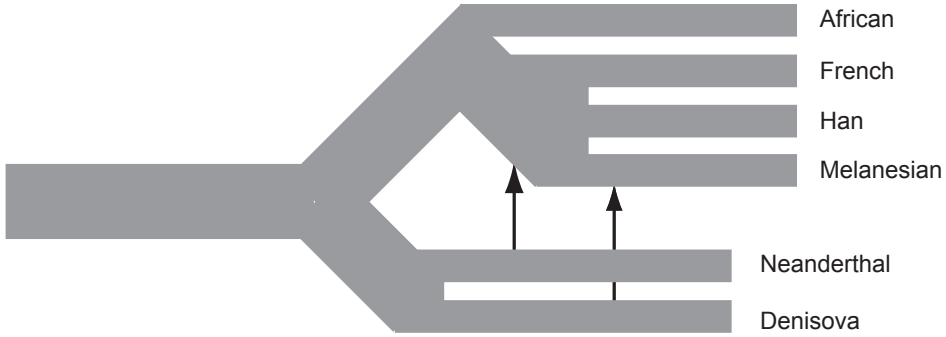

FIGURE 5.5 A population tree of humans with arrows indicating admixture from archaic human populations in the past. *Modified from Reich, D., Green, R.E., Kircher, M., et al., 2010. Genetic history of an archaic hominin group from Denisova Cave in Siberia. Nature 468, 1053–1060.*

replacement remained the dominant model for human evolution. Only with the publication of direct evidence for admixture with ancient DNA did the support for the replacement model finally begin to erode.

This erosion still did not lead to an acceptance of hypothesis testing in the area of human evolutionary studies. For example, Fig. 5.5 is based on Fig. 5.3 from Reich et al. (2010), the paper that reported the inference of admixture from the Denisovan specimen. Note that this figure presents human evolution as a population tree with just two admixture events; one from Neandertals and one inferred from the Denisovan specimen. Note that the Denisovan specimen has been elevated to the status of a long-standing and isolated evolutionary lineage of humanity despite the absence of data to support this depiction. Moreover, the modern populations of humans are depicted as isolated branches on an evolutionary tree, with Africans in particular being portrayed as a completely genetically isolated lineage from the rest of humanity for 3000 generations (75,000 years, assuming a generation length of 25 years). The authors claim that this figure is "compatible" with their data, but this statement is false since they performed no test of the testable hypothesis of a tree-like structure for modern human populations. Moreover, every time a population tree structure has been tested for humans, the hypothesis of a tree has been rejected. Indeed, the idea that Africans have been genetically isolated from the rest of the world from 75,000 years ago unto the present is clearly false as simulations based just on historical data indicate that all living humans, both Africans and non-Africans, share a common ancestor just a few thousand years ago (Rohde et al., 2004).

Figures similar to Fig. 5.5 have appeared repeatedly not only in the scientific literature, but also in newspapers and websites (Templeton, 2013). Such figures convey the message that humanity is subdivided into distinct lineages or races, even though that hypothesis has been strongly rejected by hypothesis testing. Contrast the message of discrete human lineages found in Fig. 5.5 with the continuity of human genetic diversity found in the data plot shown in Fig. 5.4 or the trellis structure shown in Fig. 5.2. Human diversity can be portrayed in a manner compatible with hypothesis testing (Fig. 5.2). If authors, reviewers, and/or editors insisted upon testing testable hypotheses, figures like Fig. 5.5 would disappear from journals and textbooks, and hopefully from newspapers and websites. Only then would our pictorial representations of human evolution educate and not mislead the general public.

THE EVOLUTIONARY AND GENETIC UNITY OF THE HUMAN SPECIES

The one overwhelming message that emerges from hypothesis testing in the area of human evolution is the importance of gene flow and admixture in keeping the human species together as a single, evolving entity, both now and in the past. This is exactly the opposite message conveyed by the OAR hypothesis (Fig. 5.1A) that had no role for gene flow or admixture, only expansion and replacement.

Although all human populations represent a single evolutionary lineage, there are some genetic differences between human populations. These differences are minor compared to the interpopulation differences observed in most other species. We are not subdivided into discrete groups and clusters, as most of our diversity displays gradual changes (eg, Fig. 5.4), including such traditional "racial" traits such as skin color. The few genetic changes that show a more discrete distribution have distributions that reflect local selective agents and not races. For example, sickle cell is found in high frequency in malarial regions and is not a disease of "blacks," as it is in high frequency in many non-African populations that live in malarial regions. The vast majority of genetic diversity in humans exists between us as individuals, not members of a population, making each of us genetically unique.

REFERENCES

Ackermann, R.R., 2002. Patterns of covariation in the hominoid craniofacial skeleton: implications for paleoanthropological models. Journal of Human Evolution 43, 167–187.

Ackermann, R.R., 2005. Variation in Neandertals: a response to Harvati (2003). Journal of Human Evolution 48, 643.

Ackermann, R.R., Smith, R.J., 2007. The macroevolution of our ancient lineage: what we know (or think we know) about early hominin diversity. Evolutionary Biology 34, 72–85.

Alperson-Afil, N., Sharon, G., Kislev, M., et al., 2009. Spatial organization of hominin activities at Gesher Benot Ya'aqov, Israel. Science 326, 1677–1680.

Armitage, S.J., Jasim, S.A., Marks, A.E., et al., 2011. The southern route out of Africa: evidence for an early expansion of modern humans into Arabia. Science 331, 453–456.

Baab, K.L., 2008. The taxonomic implications of cranial shape variation in *Homo erectus*. Journal of Human Evolution 54, 827–847.

Beaumont, M.A., Panchal, M., 2008. On the validity of nested clade phylogeographical analysis. Molecular Ecology 17, 2563–2565.

Bokma, F., van den Brink, V., Stadler, T., 2012. Unexpectedly many extinct hominins. Evolution 66, 2969–2974.

Cann, R.L., Stoneking, M., Wilson, A.C., 1987. Mitochondrial DNA and human evolution. Nature 325, 31–36.

Cavalli-Sforza, L.L., Piazza, A., 1975. Analysis of evolution: evolutionary rates, independence, and treeness. Theoretical Population Biology 37, 3–25.

Coon, C.S., 1962. The Origin of Races. Knopf, New York.

Coventry, A., Bull-Otterson, L.M., Liu, X., et al., 2010. Deep resequencing reveals excess rare recent variants consistent with explosive population growth. Nature Communications 1, 131.

Cuenca-Bescós, G., Melero-Rubio, M., Rofes, J., et al., 2011. The Early-Middle Pleistocene environmental and climatic change and the human expansion in Western Europe: a case study with small vertebrates (Gran Dolina, Atapuerca, Spain). Journal of Human Evolution 60, 481–491.

Curnoe, D., Thorne, A., 2003. Number of ancestral human species: a molecular perspective. Homo – Journal of Comparative Human Biology 53, 201–224.

Ding, Q., Hu, Y., Xu, S., Wang, J., Jin, L., 2014. Neanderthal introgression at chromosome 3p21.31 was under positive natural selection in East Asians. Molecular Biology and Evolution 31, 683–695.

Dobzhansky, T., 1944. On species and races of living and fossil man. American Journal of Physical Anthropology 2, 251–265.

Efron, B., 2013. Bayes' theorem in the 21st century. Science 340, 1177–1178.

Eriksson, A., Manica, A., 2014. The doubly conditioned frequency spectrum does not distinguish between ancient population structure and hybridization. Molecular Biology and Evolution 31, 1618–1621.

Eswaran, V., Harpending, H., Rogers, A.R., 2005. Genomics refutes an exclusively African origin of humans. Journal of Human Evolution 49, 1–18.

Fagundes, N.J.R., Ray, N., Beaumont, M., et al., 2007. Statistical evaluation of alternative models of human evolution. Proceedings of the National Academy of Sciences 104, 17614–17619.

Ferring, R., Oms, O., Agustí, J., et al., 2011. Earliest human occupations at Dmanisi (Georgian Caucasus) dated to 1.85–1.78 Ma. Proceedings of the National Academy of Sciences 108, 10432–10436.

Green, R.E., Krause, J., Briggs, A.W., et al., 2010. A draft sequence of the Neandertal genome. Science 328, 710–722.

Grun, R., Stringer, C., McDermott, F., et al., 2005. U-series and ESR analyses of bones and teeth relating to the human burials from Skhul. Journal of Human Evolution 49, 316–334.

Harding, R.M., Fullerton, S.M., Griffiths, R.C., et al., 1997. Archaic African and Asian lineages in the genetic ancestry of modern humans. American Journal of Human Genetics 60, 772–789.

Haslam, M., Roberts, R.G., Shipton, C., et al., 2011. Late Acheulean hominins at the Marine Isotope Stage 6/5e transition in north-central India. Quaternary Research 75, 670–682.

Hochberg, Z., Templeton, A.R., 2010. Evolutionary perspective in skin color, vitamin D and its receptor. Hormones – International Journal of Endocrinology and Metabolism 9, 307–311.

Howells, W.W., 1942. Fossil man and the origin of races. American Anthropologist 44, 182–193.

Huerta-Sanchez, E., Jin, X., Asan, et al., 2014. Altitude adaptation in Tibetans caused by introgression of Denisovan-like DNA. Nature 512, 194–197.

Hunt, K., 2003. The single species hypothesis: truly dead and pushing up bushes, or still twitching and ripe for resuscitation? Human Biology 75, 485–502.

Jablonski, N.G., Chaplin, G., 2013. Epidermal pigmentation in the human lineage is an adaptation to ultraviolet radiation. Journal of Human Evolution 65, 671–675.

Jin, C., Pan, W., Zhang, Y., et al., 2009. The *Homo sapiens* Cave hominin site of Mulan Mountain, Jiangzhou District, Chongzuo, Guangxi with emphasis on its age. Chinese Science Bulletin 54, 3848–3856.

Kingman, J.F.C., 1982a. The coalescent. Stochastic Processes and Their Applications 13, 235–248.

Kingman, J.F.C., 1982b. On the genealogy of large populations. Journal of Applied Probability 19A, 27–43.

Knowles, L.L., Maddison, W.P., 2002. Statistical phylogeography. Molecular Ecology 11, 2623–2635.

Larrasoña, J.C., 2012. A Northeast Saharan perspective on environmental variability in North Africa and its implications for modern human origins. In: Hublin, J.-J.M., Shannon, P. (Eds.), Modern Origins: A North African Perspective. Springer, Dordrecht, Heidelberg, New York, London, pp. 19–34.

Liu, W., Jin, C.-Z., Zhang, Y.-Q., et al., 2010. Human remains from Zhirendong, South China, and modern human emergence in East Asia. Proceedings of the National Academy of Sciences 107, 19201–19206.

Lohse, K., Frantz, L.A.F., 2014. Neandertal admixture in Eurasia confirmed by maximum-likelihood analysis of three genomes. Genetics 196, 1241–1251.

Long, J., Kittles, R., 2003. Human genetic diversity and the nonexistence of biological races. Human Biology 75, 449–471.

Lordkipanidze, D., Ponce de León, M.S., Margvelashvili, A., et al., 2013. A complete skull from Dmanisi, Georgia, and the evolutionary biology of early *Homo*. Science 342, 326–331.

Mayr, E., 1982. The Growth of Biological Thought: Diversity, Evolution, and Inheritance. The Belknap Press of Harvard University Press, Cambridge, MA.

Mayr, E., 1994. Darwin's impact on modern thought. Proceedings of the American Philosophical Society 139, 317–325.

McDougall, I., Brown, F.H., Fleagle, J.G., 2005. Stratigraphic placement and age of modern humans from Kibish, Ethiopia. Nature 433, 733–736.

Mendez, F.L., Watkins, J.C., Hammer, M.F., 2012. Global genetic variation at OAS1 provides evidence of archaic admixture in Melanesian populations. Molecular Biology and Evolution 29, 1513–1520.

Meyer, M., Fu, Q., Aximu-Petri, A., et al., 2014. A mitochondrial genome sequence of a hominin from Sima de los Huesos. Nature 403–406. Nature Publishing Group, a division of Macmillan Publishers Limited.

Meyer, M., Kircher, M., Gansauge, M.-T., et al., 2012. A high-coverage genome sequence from an archaic Denisovan individual. Science 338, 222–226.

Orlando, L., 2014. A 400,000-year-old mitochondrial genome questions phylogenetic relationships amongst archaic hominins. BioEssays 36, 598–605.

Paabo, S., 2015. The diverse origins of the human gene pool. Nature Reviews Genetics 16, 313–314.

Paixão-Côrtes, V.R., Viscardi, L.H., Salzano, F.M., Cátira-Bortolini, M., Hünemeier, T., 2013. The cognitive ability of extinct hominins: bringing down the hierarchy using genomic evidences. American Journal of Human Biology 25, 702–705.

Panchal, M., Beaumont, M.A., 2010. Evaluating nested clade phylogeographic analysis under models of restricted gene flow. Systematic Biology 59, 415–432.

Pappu, S., Gunnell, Y., Akhilesh, K., et al., 2011. Early Pleistocene presence of Acheulian hominins in South India. Science 331, 1596–1599.

Pearson, O.M., 2008. Statistical and biological definitions of "anatomically modern" humans: suggestions for a unified approach to modern morphology. Evolutionary Anthropology 17, 38–48.

Pei, S., Niu, D., Guan, Y., et al., 2015. Middle Pleistocene hominin occupation in the Danjiangkou Reservoir Region, Central China: studies of formation processes and stone technology of Maling 2A site. Journal of Archaeological Science 53, 391–407.

Popper, K.R., 1959. The Logic of Scientific Discovery. Hutchinson, London.

Potts, R., Behrensmeyer, A.K., Deino, A., Ditchfield, P., Clark, J., 2004. Small mid-Pleistocene hominin associated with East African Acheulean technology. Science 305, 75–78.

Povysil, G., Hochreiter, S., 2014. Sharing of very short IBD segments between humans, Neandertals, and Denisovans. bioRxiv. http://dx.doi.org/10.1101/003988.

Prufer, K., Racimo, F., Patterson, N., et al., 2014. The complete genome sequence of a Neanderthal from the Altai Mountains. Nature 505, 43–49.

Racimo, F., Sankararaman, S., Nielsen, R., Huerta-Sanchez, E., 2015. Evidence for archaic adaptive introgression in humans. Nature Reviews Genetics 16, 359–371.

Ramachandran, S., Deshpande, O., Roseman, C.C., et al., 2005. Support from the relationship of genetic and geographic distance in human populations for a serial founder effect originating in Africa. PNAS 102, 15942–15947.

Ray, N., Currat, M., Berthier, P., Excoffier, L., 2005. Recovering the geographic origin of early modern humans by realistic and spatially explicit simulations. Genome Research 15, 1161–1167.

Reich, D., Green, R.E., Kircher, M., et al., 2010. Genetic history of an archaic hominin group from Denisova Cave in Siberia. Nature 468, 1053–1060.

Relethford, J., 1998. Genetics of modern human origins and diversity. Annual Review of Anthropology 27, 1–23.

Relethford, J.H., 2001. Genetics and the Search for Modern Human Origins. John Wiley & Sons, New York.

Reyes-Centeno, H., Ghirotto, S., Détroit, F., et al., 2014. Genomic and cranial phenotype data support multiple modern human dispersals from Africa and a southern route into Asia. Proceedings of the National Academy of Sciences 111, 7248–7253.

Rightmire, G.P., 2009. Middle and later Pleistocene hominins in Africa and Southwest Asia. Proceedings of the National Academy of Sciences 106, 16046–16050.

Rohde, D.L.T., Olson, S., Chang, J.T., 2004. Modelling the recent common ancestry of all living humans. Nature 431, 562–566.

Rohlf, F.J., 1993. NTSYS-pc: Numerical Taxonomy and Multivariate Analysis System. Version 1.80 Exeter Software, Setauket, NY.

Sankararaman, S., Mallick, S., Dannemann, M., et al., 2014. The genomic landscape of Neanderthal ancestry in present-day humans. Nature 507, 354–357.

Scally, A., Durbin, R., 2012. Revising the human mutation rate: implications for understanding human evolution. Nature Reviews Genetics 13, 745–753.

Scott, G.R., Gibert, L., 2009. The oldest hand-axes in Europe. Nature 461, 82–85.

Scozzari, R., Massaia, A., Trombetta, B., et al., 2014. An unbiased resource of novel SNP markers provides a new chronology for the human Y chromosome and reveals a deep phylogenetic structure in Africa. Genome Research 24, 535–544.

Seguin-Orlando, A., Korneliussen, T.S., Sikora, M., et al., 2014. Genomic structure in Europeans dating back at least 36,200 years. Science 346, 1113–1118.

Simmons, T., 1999. Migration and contact zones in modern human origins: baboon models for hybridization and species recognition. Anthropologie 37, 101–109.

Smouse, P.E., 1998. To tree or not to tree. Molecular Ecology 7, 399–412.

Smouse, P.E., 2000. Reticulation inside the species boundary. Journal of Classification 17, 165–173.

Soares, P., Alshamali, F., Pereira, J.B., et al., 2012. The expansion of mtDNA Haplogroup L3 within and out of Africa. Molecular Biology and Evolution 29, 915–927.

Stringer, C.B., Andrews, P., 1988. The origin of modern humans. Science 239, 1263–1268.

Takahata, N., Lee, S.-H., Satta, Y., 2001. Testing multiregionality of modern human origins. Molecular Biology and Evolution 18, 172–183.

Templeton, A.R., 1994. "Eve": hypothesis compatibility versus hypothesis testing. American Anthropologist 96, 141–147.

Templeton, A.R., 1998a. Human races: a genetic and evolutionary perspective. American Anthropologist 100, 632–650.

Templeton, A.R., 1998b. Nested clade analyses of phylogeographic data: testing hypotheses about gene flow and population history. Molecular Ecology 7, 381–397.

Templeton, A.R., 2002. Out of Africa again and again. Nature 416, 45–51.

Templeton, A.R., 2004a. A maximum likelihood framework for cross validation of phylogeographic hypotheses. In: Wasser, S.P. (Ed.), Evolutionary Theory and Processes: Modern Horizons. Kluwer Academic Publishers, Dordrecht, The Netherlands, pp. 209–230.

Templeton, A.R., 2004b. Statistical phylogeography: methods of evaluating and minimizing inference errors. Molecular Ecology 13, 789−809.

Templeton, A.R., 2006. Population Genetics and Microevolutionary Theory. John Wiley & Sons, Hoboken, New Jersey.

Templeton, A.R., 2007. Perspective: genetics and recent human evolution. Evolution 61, 1507−1519.

Templeton, A.R., 2008. Nested clade analysis: an extensively validated method for strong phylogeographic inference. Molecular Ecology 17, 1877−1880.

Templeton, A.R., 2009a. Statistical hypothesis testing in intraspecific phylogeography: nested clade phylogeographical analysis vs. approximate Bayesian computation. Molecular Ecology 18, 319−331.

Templeton, A.R., 2009b. Why does a method that fails continue to be used: the answer. Evolution 63, 807−812.

Templeton, A.R., 2010. Coherent and incoherent inference in phylogeography and human evolution. Proceedings of the National Academy of Sciences 107, 6376−6381.

Templeton, A.R., 2013. Biological races in humans. Studies in History and Philosophy of Biological and Biomedical Sciences 44, 262−271.

Templeton, A.R., 2015. Population biology and population genetics of Pleistocene hominins. In: Henke, W., Tattersall, I. (Eds.), Handbook of Paleoanthropology. Springer, Heidelberg, New York, Dordrecht, London, pp. 2331−2370.

Templeton, A.R., Routman, E., Phillips, C., 1995. Separating population structure from population history: a cladistic analysis of the geographical distribution of mitochondrial DNA haplotypes in the Tiger Salamander, *Ambystoma tigrinum*. Genetics 140, 767−782.

Templeton, A.R., Sing, C.F., 1993. A cladistic analysis of phenotypic associations with haplotypes inferred from restriction endonuclease mapping. IV. Nested analyses with cladogram uncertainty and recombination. Genetics 134, 659−669.

Templeton, A.R., Weiss, K.M., Nickerson, D.A., Boerwinkle, E., Sing, C.F., 2000. Cladistic structure within the human lipoprotein lipase gene and its implications for phenotypic association studies. Genetics 156, 1259−1275.

Thackeray, J.F., 2007. Approximation of a biological species constant? South African Journal of Science 103, 489.

Thackeray, J.F., Bellamy, C.L., Bellars, D., et al., 1997. Probabilities of conspecificity − application of a morphometric technique to modern taxa and fossil specimens attributed to *Australopithecus* and *Homo*. South African Journal of Science 93, 195−196.

Van Arsdale, A.P., Wolpoff, M.H., 2013. A single lineage in early Pleistocene *Homo*: size variation continuity in early Pleistocene *Homo* crania from East Africa and Georgia. Evolution 67, 841−850.

Vanhaeren, M., d'Errico, F., Stringer, C., et al., 2006. Middle Paleolithic shell beads in Israel and Algeria. Science 312, 1785−1788.

Vernot, B., Akey, J.M., 2014. Resurrecting surviving Neandertal lineages from modern human genomes. Science 343, 1017−1021.

Villmoare, B., 2005. Metric and non-metric randomization methods, geographic variation, and the single-species hypothesis for Asian and African *Homo erectus*. Journal of Human Evolution 49, 680−701.

Wall, J.D., Yang, M.A., Jay, F., et al., 2013. Higher levels of Neanderthal ancestry in East Asians than in Europeans. Genetics 194, 199−209.

Weidenreich, F., 1946. Apes, Giants, and Man. University of Chicago Press, Chicago.

Wolpoff, M., Thorne, A., 1991. The case against Eve. New Scientist 22, 37−41.

Wolpoff, M., Thorne, A.G., Smith, F.H., Frayer, D.W., Pope, G.G., 1994. Multiregional evolution: a world-wide source for modern human populations. In: Nitecki, M.H., Nitecki, D.V. (Eds.), Origins of Anatomically Modern Humans. Plenum Press, New York, pp. 175−200.

Wolpoff, M.H., 1996. Interpretations of multiregional evolution. Science 274, 704−706.

Wolpoff, M.H., Caspari, R., 2000. The many species of humanity. Przeglad Antropologiczny − Anthropological Review 63, 3−17.

Wolpoff, M.H., Hawks, J., Caspari, R., 2000. Multiregional, not multiple origins. American Journal of Physical Anthropology 112, 129−136.

Wolpoff, M.H., Spuhler, J.N., Smith, F.H., et al., 1988. Modern human origins. Science 241, 772−773.

Workman, P.L., Blumberg, B.S., Cooper, A.J., 1963. Selection, gene migration and polymorphic stability in a U.S. White and Negro population. American Journal of Human Genetics 15, 71−84.

Chapter 6

Human Population Variability and Its Adaptive Significance

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LIST OF ABBREVIATIONS

AFA African American
AFR African
AIM Ancestry informative marker
AJ Ashkenazi Jew
ASA Asian American
Bp Base pair (the elementary unit of the DNA sequence)
CV Common variant
EUR European
EURA European American
GWAS Genome-wide association study
HGDP Human Genome Diversity Project
HISP Hispanic
LFV Low- frequency variant
MAF Minor allele frequency
ME Middle East
NAM Native American
OOA Out of Africa
PCA Principal component analysis
RV Rare variant
SEA South East Asian
SRA Self-reported ancestry
SV Structural variation

Baby-boomer biologists (myself included) have lived a professional dream. Their whole career has been accompanied with the advent and incredible improvement of amazing technologies. All the more admirable is the genius of our elders, Gregor Mendel, Thomas Hunt Morgan, and Theodozius Dobzhansky, among many others, who founded genetics and population genetics with only peas and fruit fly salivary gland chromosomes to sink their teeth into. From the very start, the spoiled baby boomers have been able to play with isoenzyme markers, and, not long after, with a wealth of DNA technologies: restriction fragment length polymorphism, random amplified polymorphic DNA, amplification fragment length polymorphism, microsatellites, and the alike. To spoil us even more, we have benefited from the advent and exponential development of computers. All these breakthroughs have been massively applied to the study of human genetics and evolution. The field is a burning one. Several key papers come out weekly, and data published only a few years ago might be severely outdated. This is why in the present chapter, I have attempted to privilege the most recent advances in the field. The chapter focuses on population rather than individual variation. It does not aim to be a comprehensive review of the field, but rather, to catch the main currents of research in the field.

A MANKIND POPULATION GENETICS FRAMEWORK FOR APPLIED RESEARCH

Where applied research is concerned (exploring genes and variants of interest), it is convenient to first draw an exhaustive population genetic framework of the species under study in its whole ecogeographical range. Then the relevant genes and variants are mapped onto this general picture. This makes it possible to compare the specific evolution of these genes to the overall evolution of the whole species (phylogenetic character mapping; Avise, 2004). This approach is highly recommended when performing applied research in humans (Tibayrenc, 2007a). Moving toward this goal, a wealth of data have been gathered by three major international projects, namely the HapMap project (http://hapmap.ncbi.nlm.nih.gov/), the Human Genome Diversity project (HGDP; http://www.hagsc.org/hgdp/), and the 1000 Genomes Project (http://www.1000genomes.org/). These multicontinental projects are completed by geographically restricted programs, such

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00006-5

as the "UK10K consortium" (http://www.uk10k.org/). These projects, together with many outstanding pioneering studies, have made it possible to reach the main results summarized in the following sections.

Most Genetic Variation Occurs Within Continental Groups

Before direct DNA analysis was possible, the only reliable genetic tools were blood groups and isoenzymes. These pioneering markers made it possible to evidence a key fact that has been fully confirmed by the most recent technologies: taking the set of markers as a whole, when considering the native inhabitants of major continental regions (Europe, the Americas, Africa, Asia, and Oceania), the intragroup variability far exceeds the intergroup variability: about 0.85 versus 0.15 (Lewontin, 1972). Intergroup differences are conveniently measured by the *F*st statistic (Wright, 1978; see box 1). This remarkable feature has been confirmed by all subsequent studies, based on various molecular markers, with some fluctuations, but always the same strong tendency: 30 microsatellites and 79 RFLP: $Fst = 0.10$ (Barbujani et al., 1997); microsatellites: 0.10; RFLP: 0.13; Alu insertion sequences: 0.14 (Lachance and Tishkoff, 2013); gene sequences: 0.159; microsatellites: 0.057 (Long et al., 2009); Alu insertion sequences: 0.127 (Romualdi et al., 2002); microsatellites: 0.153 (Rosenberg et al., 2005); and single nucleotide polymorphisms (SNPs): 0.052 (Auton et al., 2009); 0.132 (Shriver et al., 2004). Depending on the polymorphism considered, Jakobsson et al. (2008) have found different figures for percentages of variants that are not shared among continents: the value for SNPs roughly fitted the classical feature (18.7%). However, for haplotype clusters and copy-number variants (CNVs), the results were 87.57% and 38.81%, respectively. These figures do not represent *F*st statistics, strictly speaking. However, they show that the percentage of unshared polymorphisms among continental regions is highly dependent upon the polymorphism considered. Conrad and Hurles (2007) found a $Fst = 0.11$ for CNVs.

This result concerning *F*st patterns among populations involve common variants (CVs; frequency $\geq$5%) and what can be called "historical markers," markers that do not undergo natural selection, whose polymorphism is proportional to the time elapsed since population separation. The pattern is very different when rare variants (frequency $\leq$0.5%) and adaptive polymorphisms are considered (see later in this chapter and in Chapter 38).

Clines, Clusters, Clinal Clusters, Trees?

In spite of this limited intergroup variability, another strong result has emerged since human populations started to be surveyed with genetic markers: populations could be reliably grouped according to their geographical origin. This was already possible with isoenzymes, although this marker has a relatively limited resolution and undergoes homoplasy. Fig. 6.1 shows a phylogenetic tree depicting the genetic distances for 11 isoenzyme loci and 11 blood groups among major human continental groups (Nei, 1978). This early study can be considered as the first, pioneering attempt to build an overall genealogical tree of the genetic diversity of our species. A more recent study, relying on 29 isoenzyme loci, gave a more precise picture of this diversity (Nei and Roychoudhury, 1993, Fig. 6.2). General clustering in both studies match the generally recognized geographical populations well (Europeans, Asians, Africans, Native Americans, Oceanians). Both trees show that Africans constitute a specific cluster that is clearly separated from another cluster encompassing all non-African populations. These pioneering studies using rustic, low-resolution markers, and very simple phylogenetic methods show that it is untrue to state that geographical groupings can be evidenced only through the use of carefully selected modern markers and sophisticated analyses (Jordan, 2008, Chapter 6). The results of these early studies have been confirmed by many others relying on various markers and different population samples. Modern DNA-based tools greatly refined the picture, but did not upset the results gathered by protein markers (Cavalli-Sforza and Feldman, 2003). Hierarchical relationships among geographical groups have been slightly modified by more recent studies, and at nowadays, modern DNA tools are able to accurately identify the region of origin of individuals, not only populations, which was impossible with isoenzymes and blood groups. However, the main features (clear groupings according to geographical ancestries, and separation between Africans and non-Africans) remain (Fig. 6.3).

This tree-based approach has been criticized because (1) "it has been falsified whenever tested, so this practice is scientifically indefensible"; (2) "it is also socially irresponsible as these pictorial representations of human evolution have more impact on the general public than nuanced phrases in the text of a scientific paper" (Templeton, 2013). However, tree representations of human diversity are widely used by many, if not most, authors working in the field and constantly yield convergent results. It is obvious that such trees do not show, strictly speaking, clades. They should be merely considered as population trees, a convenient visual summary of our species' genetic diversity. Such trees do not mean that geographical populations are strictly separated; they are not. Ethical and semantic issues concerning human diversity are presented in detail in Chapter 38.

Together with this tree approach, there is now a tendency to use "unsupervised," model-free, nonphylogenetic

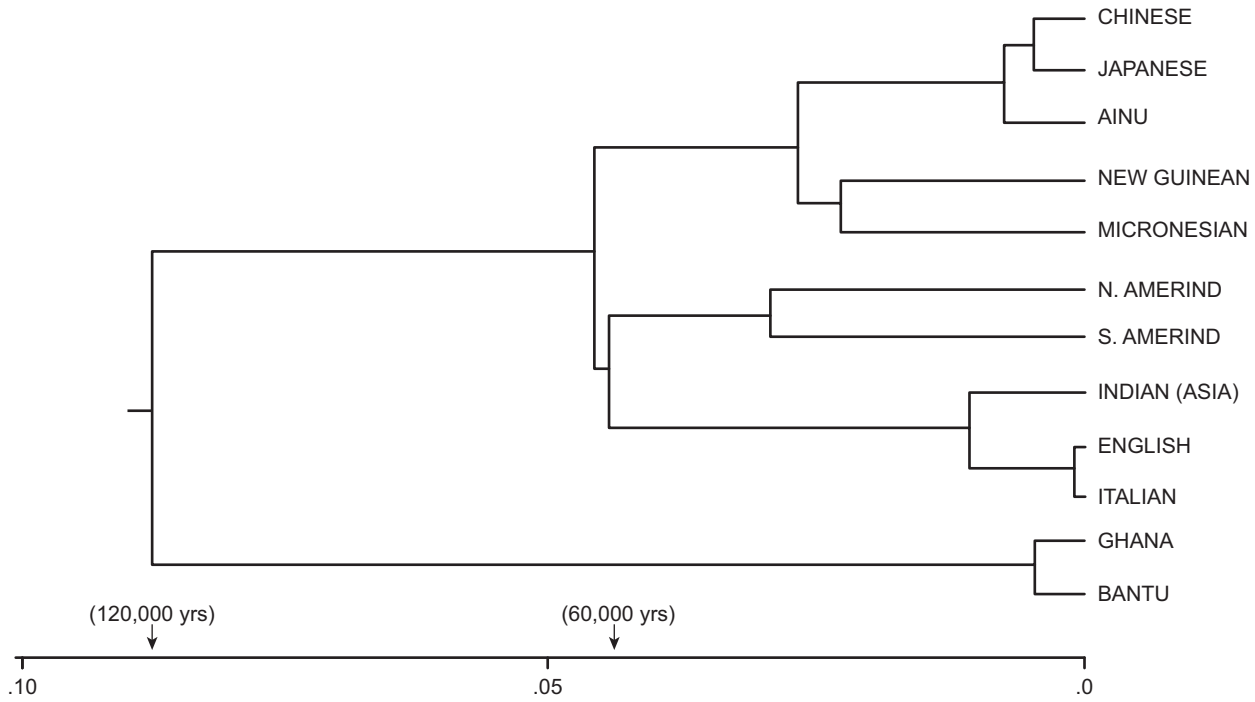

FIGURE 6.1 A phylogenetic tree of the main human ethnic groups designed from 11 isoenzyme markers and 11 blood groups. *Nei, M., 1978. The theory of genetic distance and evolution of human races. Japanese Journal of Human Genetics 23, 341–369.*

methods, in which the unit of analysis is not the population (defined a priori), but instead the individual: principal component analysis (PCA), ADMIXTURE, FRAPPE (Alexander et al., 2009), and STRUCTURE (Pritchard et al., 2000). These methods, although they are rooted in totally different assumptions, give quite convergent results with trees and phylogenies. They present the advantage of yielding a precise estimation of admixture rates within populations. STRUCTURE infers a subdivision of the samples into K clusters and explores which K number fits the data best. Individuals are ranked into given clusters. They can belong to several clusters, with membership coefficients summing to 1 across clusters (Rosenberg et al., 2002). As is the case for any approach, the reliability of the results is dependent upon sampling quality (populations and molecular markers). In the seminal article by Rosenberg et al. (2002), based on 1056 individuals worldwide (from the panel of the HGDP) and 377 microsatellite loci, STRUCTURE uncovered six major clusters, of which five corresponded to major continental regions (Africa, Europe, the part of Asia south and west of the Himalayas, East Asia, Oceania, and the Americas). The sixth grouping largely corresponded to the Kalash, an Indo-Iranian-speaking population of Pakistan, whose origin is debated. It has been claimed that his clustering pattern was partly artifactual, due to sampling biases (Serre and Pääbo, 2004). However, this hypothesis has been refuted by Hunley et al. (2009) and by the authors themselves, who fully confirmed their results with a broader range of genetic markers (783 microsatellite loci and 210 insertion-deletion sequences ["indels": see CNV]) (Rosenberg et al., 2005). In the latter study, the role played by geographical dispersion was clarified: within the clusters, genetic distances are correlated with geographical distances (clinal variation). However, among clusters, major geographical obstacles (the Sahara, oceans, Himalayas) play a role, and have an impact on genetic distances equivalent to 3100 km. The authors concluded that both clines and clusters were evidenced in their study. Pigliuci (2013) has emphasized the fact that five clusters could appear somewhat arbitrary, since, according to the level of analysis, K could be either 3 or 5. However, $K = 5$ is the figure that fits the data better (Cavalli-Sforza, 2007). Tishkoff and Kidd (2004) characterized 37 populations with 80 loci (41 haplotyped loci, 36 biallelic loci, and three short tandem repeat polymorphisms, and found the same continental groups as Rosenberg et al. (2002, 2005)). Interestingly, African-Americans (AFAs) are clearly within the African cluster, although it is generally considered that AFAs have a European admixture rate ranging from 7% to 20%, depending on the location (González Burchard et al., 2003). Although in their study, "clusters correlate with the common concept of 'races,' " the authors cautiously warned that "the distribution of genetic variation is quasi continuous in clinal patterns related to geography." They stated that if there were more intermediary populations, clustering

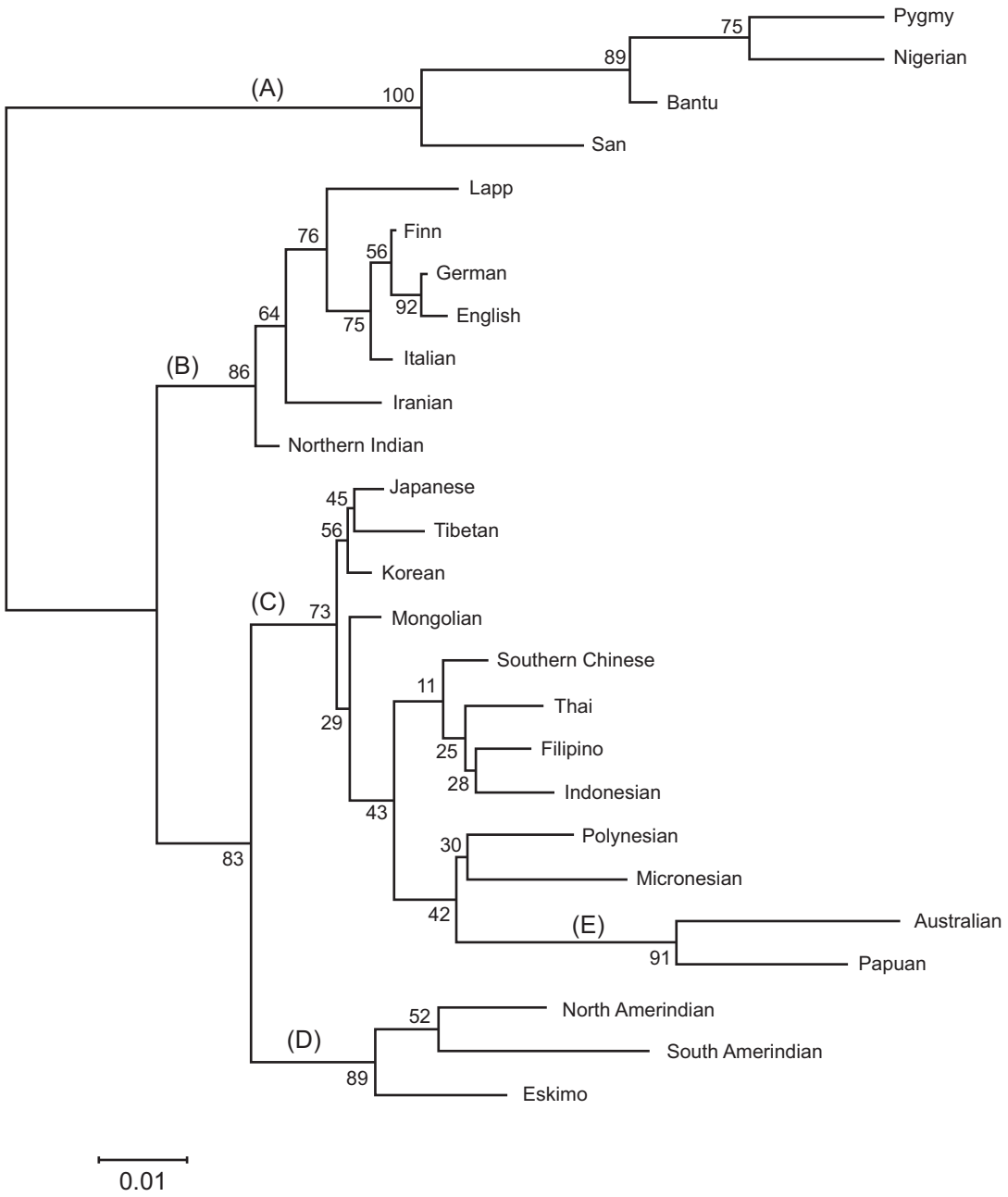

FIGURE 6.2 A phylogenetic tree of the main human ethnic groups designed from 29 isoenzyme markers *(after Nei, M., Roychoudhury, A.K., 1993. Evolutionary relationships in human populations on a global scale. Molecular Biology and Evolution 10, 927–943.)*. Subdivisions are supported by strong bootstrap values, although they do not correspond to strictly defined clades.

would be less clear. Still the fact remains that, with such large and diversified samples, the presence of the five major continental populations seems to be robust. There is a clear phylogenetic signal among geographically separated populations, although they are not strictly separated and have diverged from one another relatively recently (the "out-of-Africa" [OOA] hypothesis, generally dated at −50,000 to −60,000 years). The five major continental populations have been corroborated by many different markers. The polymorphism of structural variation (SV; see further) is congruent with that of SNPs (Armengol et al., 2009; Conrad and Hurles, 2007; Sudmant et al., 2015a). Contrary to what is stated by Barbujani and Colonna (2010), in the study reported by Jakobsson et al. (2008), the phylogenies inferred from SNP, CNV and haplotypes show fair parity for the major continental groupings, and are

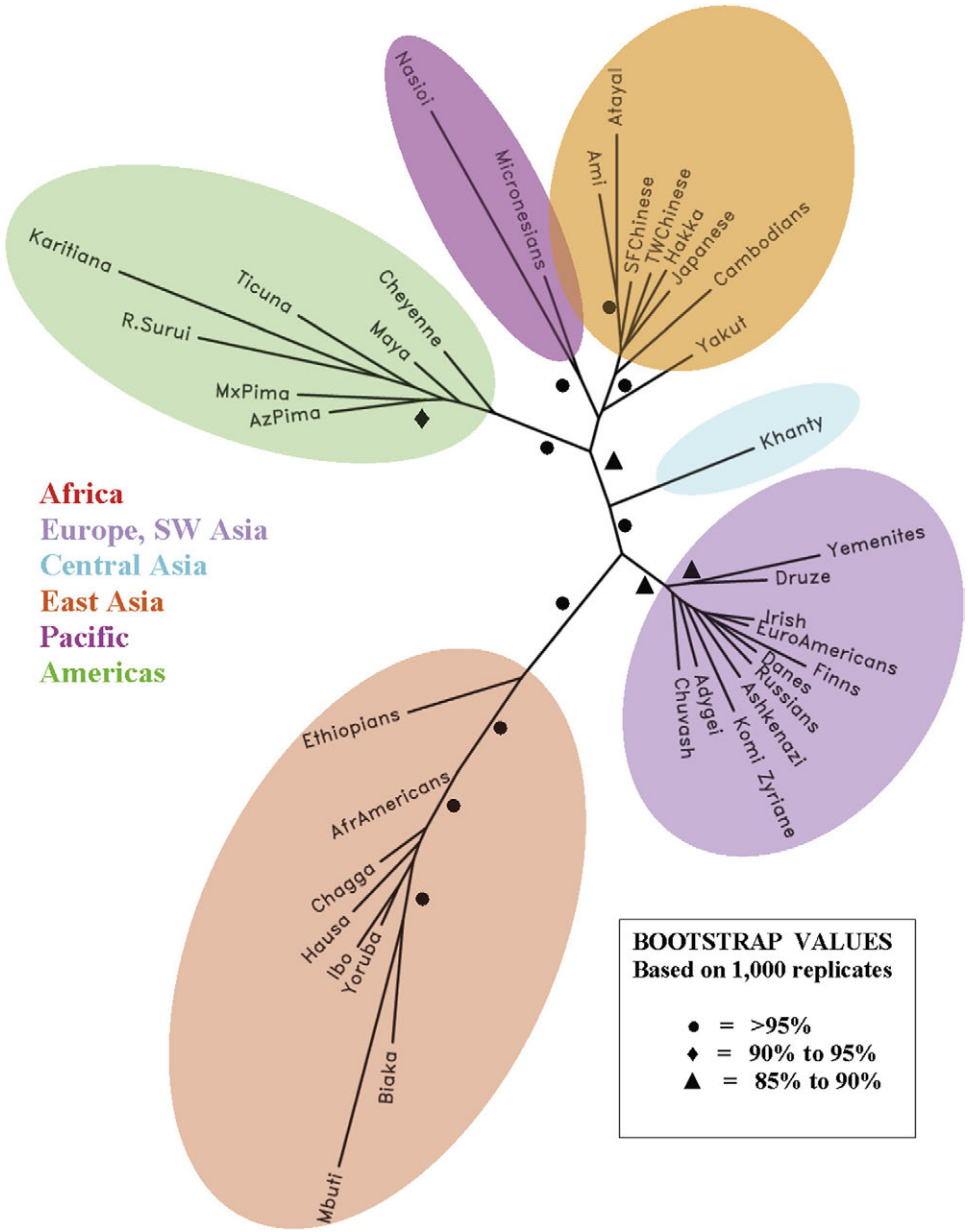

FIGURE 6.3 Least-squares tree for 37 populations based on 80 independent loci (41 haplotyped loci, 36 biallelic loci, and 3 short tandem repeat polymorphisms [STRPs]) (Tishkoff and Kidd, 2004).

corroborated by nonphylogenetic, Bayesian clustering (Fig. 6.4). The CNV phylogeny differs only in the hierarchization of lower branches.

Li et al. (2008) typed 938 individuals from the HGDP with 650,000 common SNPs. With the FRAPPE software, at $K = 5$, they found the same groupings as Rosenberg et al. (2002, 2005). At $K = 7$, the populations clustered into Africa, the Middle East, Europe, Central/South Asia, East Asia, Oceania, and America. This clustering pattern was fully confirmed by a maximum likelihood tree. López Herráez et al. (2009), with nearly 1 million SNPs, found an optimum $K = 6$ on HGDP populations as well. Continental groupings were Africa, America, Europe/North Africa/Middle East, Central and South Asia, and East Asia and Oceania. With a very specific sample based on the POPRES collection (http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000145.v4.p2), encompassing admixed and urban populations identified by self-reported ancestry (SRA), by using 443,434 SNPs, Auton et al. (2009) found groupings that parallel those of the HapMap and HGDP samples. Long et al. (2009) found that trees based on either sequences or microsatellites were in agreement with each other and with previously published trees.

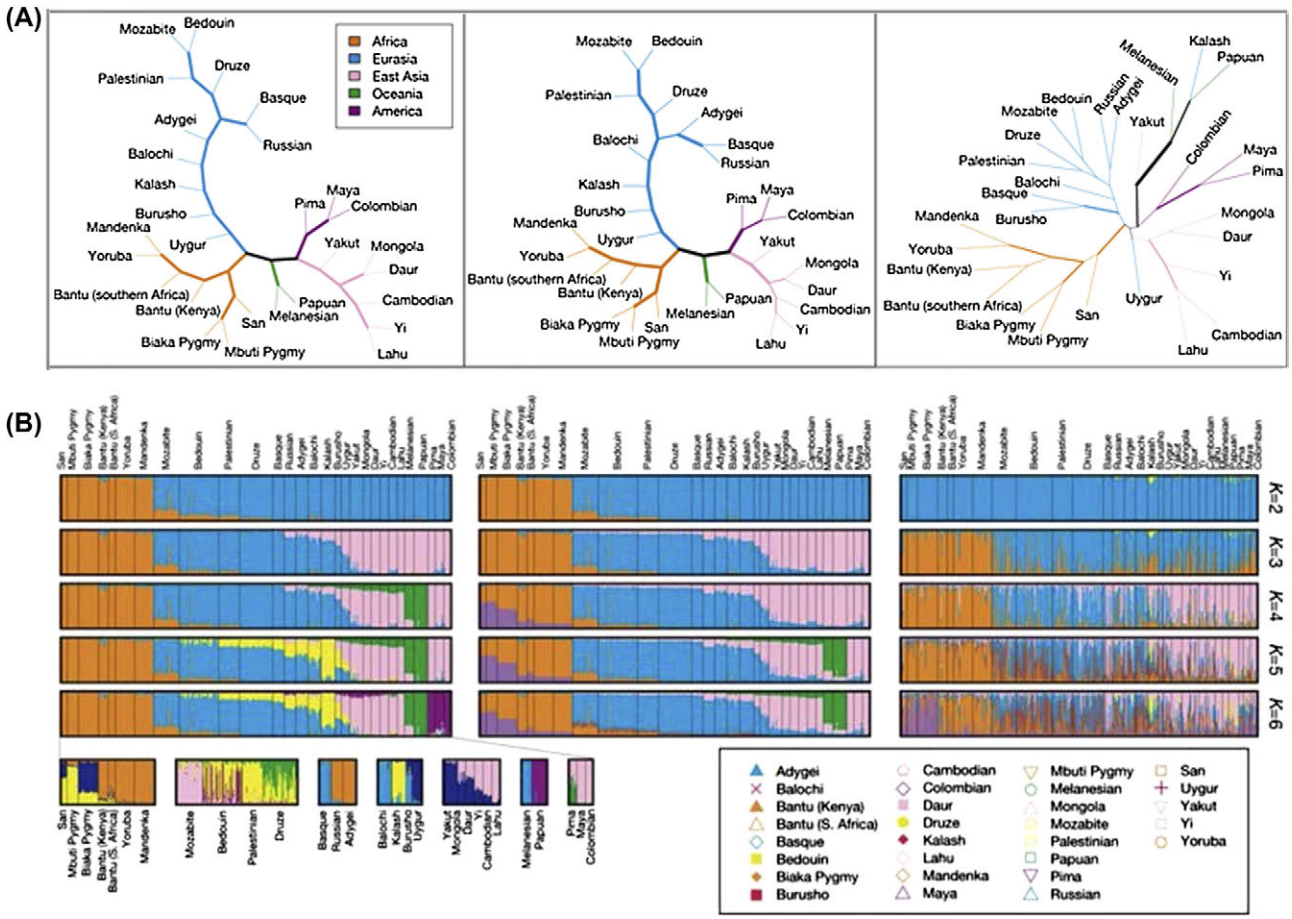

FIGURE 6.4 (A) Neighbor-joining trees of population relationships. Internal branch lengths are proportional to bootstrap support. *Lines of intermediate thickness* represent internal branches with more than 50% bootstrap support, and the *thickest lines* represent more than 95% support. (B) Population structure inferred by Bayesian clustering. Each individual is shown as a *thin vertical line* partitioned into K colored components representing inferred membership in K genetic clusters. The bottom row provides inferred population structure for each geographic region (Jakobsson et al., 2008).

This convergence of various methods and sampling strategies suggests that this pattern (clustering following major continental ancestries) is a robust one, according to one criterion of the "principles of genealogical concordance," namely the congruence across independent gene trees in delineating the geographical position of a major phylogeographical break between sets of populations (Avise, 2004). The convergence between phylogenetic and nonphylogenetic clustering approaches, between radically different kinds of markers (isoenzymes, microsatellites, SNPs, haplotypes, CNVs, sequences) is an especially telling illustration of the robustness of this clustering pattern (Tibayrenc and Ayala, 2012).

The pattern is clinal when migration routes throughout continents are used as a sampling strategy (Barbujani and Colonna, 2010). However, this approach imperfectly reflects the overall structure of populations. At the level of worldwide populations, major geographical obstacles (Himalaya, oceans, Sahara) introduce some clustering together with the clinal variation (Rosenberg et al., 2005), as already noted by Dobzhansky (1966). Shiao et al. (2012) have proposed the concept of "clinal classes" to describe this pattern.

The clustering is at first glance somewhat unexpected when considering the limited intergroup differences presented earlier. This is explained by the fact that Fst statistics considers each locus independently, while the allelic frequency differences among geographical populations are correlated (Mitton, 1977, 1978; Edwards, 2003; Jorde and Wooding, 2004).

Now this gross clustering pattern represents a bird's eye view, so to speak, of the genetic variability of our species. More detailed studies uncover a great deal of additional stratification within each of the five major populations, which has immense evolutionary and biomedical implications.

Russian Dolls Everywhere

Francisco J. Ayala and I have proposed the "Russian doll model" (Tibayrenc and Ayala, 2013) for microbial pathogens. Briefly, the model says that within clusters, there are smaller clusters, within which there are even smaller clusters, etc. It looks like the same obtains in human populations. When microbes are concerned, this pattern is explained by in-built genetic properties leading to predominant clonal evolution. In humans, the dolls are caused mainly by allopatry, additionally by cultural factors, in particular languages (Cavalli-Sforza et al., 1992). It seems that separation by distance is able to operate at very small geographical scales. This human "micro-population genetics" has been made possible by the advent of markers with an increased resolution (SNPs, microsatellites) and a massive use of them: studies relying on several hundreds of thousands of markers are today not exceptional. Stratification and Russian doll patterns within main geographical populations are chiefly due to low-frequency variants ("Goldilocks variants"; frequency 0.5−5%; Nelson et al., 2012) and even more, rare variants (frequency $\leq$0.5%). As a matter of fact, the rarer the variant, the more its tendency to be geographically localized. This explains why stratification within populations can be strong even when *F*st among major populations are not. *F*st are computed from CVs. Allele sharing of rare variants is limited, even between close populations (Mathieson and McVean, 2012). As we will see below, rare variants have a strong influence on phenotypic polymorphisms.

Lewontin and Hartl (1991) warned about the risk of not taking into account additional genetic structuration within major ethnic groups in forensic analyses: the rough US census categories (African, European, Asian, Native Americans, etc.) are far from being genetically homogeneous.

Elhaik et al. (2014) applied the geographic population structure algorithm to the study of populations collected in the framework of the genographic project (https://genographic.nationalgeographic.com/). The populations were selected for not having undergone migrations for several centuries. The authors were able to assign 83% of individuals to their birth country, and 66% to specific regions. In the specific case of Sardinia, 25% of individuals were assigned to their village of origin, and most of the rest within 100 km of their birthplace.

Using SNPs, Leslie et al. (2015) characterized 2039 rural British individuals and 6209 individuals from other European countries, all of European ancestry. The British subjects were selected so that their four grandparents had lived in the same area, in order to lower the impact of very recent migrations. The authors found a clear structuration linked to geography and natural obstacles in both the United Kingdom and other European countries. A clear clustering pattern was evidenced in the British sample. The genetic contribution of the Saxons was estimated at 10−40%. Scandinavian contribution was limited except on Okney Island. While English people appeared to be genetically homogeneous, individuals of Celtic ancestry were not. Data are consistent with ancestry of British people mainly from Germany, Belgium, and Northwest France. Another study (The UK10K Consortium, 2015) relying on a different sampling strategy (people were not selected according to their grandparents' birthplace) still found that populations were structured according to rare and very rare variants, but to a lesser extent than in the study by Leslie et al. (2015). This shows that modern times increasingly cause growing homogenization in people.

López Herráez et al. (2009) found a clear structuration of European populations, correlated to geographical distance. This correlation was not observed in Africa and the Americas, although the populations of these regions were obviously genetically heterogenous. In Africa and the Americas, populations instead clustered according to the ethnic origin (Bantus, Yorubas, San, Mbuti, and Biaka Pygmies in Africa; Piapoco, Curripaco, Maya, Pima, Karitiana, and Suriu in the Americas). Interestingly, these results were not changed when retrieving the SNPs with the 10% highest *F*st values. This shows that these Russian doll patterns reflect genome-wide properties, and are not caused by just a few, highly differentiated SNPs.

Moreno-Estrada et al. (2014) surveyed 511 Native Mexicans pertaining to 20 different tribes, and admixed Mexicans from Mexico and Los Angeles, with 1 million SNPs. They found that Native Mexican genetic variability followed a Northwest−Southeast cline. Interestingly, this particular population structure was conserved in admixed Mexicans from Mexico, but not in those from Los Angeles.

Nelson et al. (2012) have found that rare variants in Europe were stratified following a north-south gradient. Finnish populations had one-third of the rare variant diversity of Southern Europeans.

By typing 3192 individuals of the POPRES collection with 500,000 SNP, Novembre et al. (2008) and Novembre and Ramachandran (2011) found that genetic polymorphism closely followed geography in Europe. Iberic peninsula, Italy, Southeast Europe, Turkey, and Cyprus were clearly individualized. Micro-population genetics was able to go down to the village scale, the authors said. Interestingly, German-, French-, and Italian-speaking Swiss were separated from one another, which suggested that linguistic separation, together with allopatry, plays a role in Russian dolling.

The work by Longobardi et al. (2015) seems to support this hypothesis. The authors found significant correlations between genomic and linguistic diversity in Europe (both Indo-European and non-Indo-European languages). Language appeared to be a better predictor of genomic differences than geography. Similarly, Wang et al. (2012)

found that Bantu-speaking populations were grouped together by genetic markers, even if they were separated by large geographical distances.

This Russian doll structure explains why the number of races described by classical anthropology may vary greatly from one author to another, depending on the level of resolution the authors wish to address. Vallois (1976) describes four "groups" (also called *grand races*, or great races) and 27 races. He also notes that some authors describe "subraces" and "populations." This terminology is a reflection of the Russian doll structure of human populations. As stated by Dobzhansky (1966), differences among races are objective facts, while the number of races the authors describe is a matter of convenience and depends upon the goal of the study. These points will be extensively discussed in Chapter 38.

The concept of "clinal classes" (Shiao et al., 2012; Shiao, 2014) clearly describes this pattern. The clinal classes are compared to watersheds, some ones being large (the Mississippi watershed), other ones being smaller, within the large ones. The STRUCTURE approach, with its flexible number of K categories, makes it possible to evidence large and lesser clinal classes, if the marker's level of resolution and the population sampling are sufficient.

The main geographic clusters of the human species and their Russian-doll lesser subdivisions are to some extent similar to the "near-clade" concept we forged to describe the genetic variability of human pathogens (Tibayrenc and Ayala, 2012): evolutionary lines imperfectly separated from one another, whose discreteness is clouded by occasional genetic exchange. Now again in microbes, genetic isolation is caused by predominant clonal evolution, while in humans, it is due to isolation by distance and geographical obstacles, reinforced by cultural differences. In both cases, humans and micropathogens, imperfect discreteness makes that applying excessively strict cladistic demands would be misleading. For pathogens, we have proposed to use a flexible phylogenetic approach instead, based on a congruence criterium, namely that adding relevant data will lead to increasing evidence, whenever the working hypothesis is valid. This works with human genetic data: the use of more and more discriminative and diversified markers on more and more populations has made the overall picture of mankind genetic variability far more precise.

All Admixed

Not only do human populations exhibit this highly stratified Russian doll structure, but they also prove to have undergone thorough and complex admixtures. This corroborates the view of classical anthropology, which divided human populations into "primary races" resulting only from the action of evolutionary forces, and "secondary races" resulting from long-continued intermixture of two or more primary races within an area of relative isolation. Secondary races (admixed) were considered as representing most of the present populations in the world, while primary races were considered as relictual populations (Hooton, 1926). This does not mean that present human populations are homogeneous, either phenotypically or genetically. On the contrary, the data summarized above show that they are clearly diversified. Nevertheless, extensive genetic exchange throughout history has been the rule rather than the exception. "Pure" populations (primary races; Hooton, 1926) virtually do not exist.

The revolutionary use of ancient DNA makes it possible to reliably uncover ancient admixture. It has evidenced that the European populations of today are a result of a mixture of three ancient populations related to Mesolithic Western Hunter-Gatherers (WHG), Early European Farmers (EEF), and steppe pastoralists (Yamnaya)/Ancient North Eurasians (ANE) (Haak et al., 2015; Lazaridis et al., 2014; Mathieson et al., 2015). Present European people have different dosages of the ancestral populations: in the Baltic region, WHG ancestry is stronger, and there is only 30% of EEF ancestry. In Mediterranean populations the EEF ancestry is 90% (Lazaridis et al., 2014). The Yamnaya ancestry is stronger in Northern than in Southern Europe (Haak et al., 2015).

Gallego et al. (2015) have sequenced the DNA of a 4500-year-old Ethiopian hunter-gatherer. By comparing this sequence with that of present-day Ethiopians and other Africans, they found an indication of ancient migrations from the Middle East to remote people such as the South African Khoisans and Congo Pygmies.

All populations studied by Elhaik et al. (2014) within the framework of the genographic project proved to be admixed. The least admixed population was the Yoruba from Nigeria. Puerto Rico and the Bermudas exhibited the highest rate of admixture.

In the framework of the African Genome Variation project, Gurdasani et al. (2015) characterized the dense genotypes from 1481 individuals and whole-genome sequences from 320 individuals across sub-Saharan Africa. They found complex, regionally distinct hunter-gatherer and Eurasian admixture across sub-Saharan African populations.

Hellenthal et al. (2014) have analyzed 1490 individuals from worldwide populations, including 53 populations from the HGDP. Populations were typed with 474,491 autosomal SNPs. The authors found complex patterns of admixture in most populations, and were able to corroborate historical events such as the Bantu expansion, the Arab slave trade, and the Mongol empire.

The so-called Hispanic US census category is a set of admixed populations, with European, Native American, and African ancestries (Risch et al., 2002). The percentage

of these ancestries varies among countries and populations. In Colombia, the European contribution is stronger in the Andean part of the country, while the African ancestry is stronger on the coast (Cardona-Castro et al., 2015).

Lastly, the percentage of European ancestry in AFAs generally ranges from 7% to 20% (González Burchard et al., 2003).

Ancestry informative markers (AIM) make it possible to evaluate the degree of admixture even at the individual level (Sarich and Miele, 2004, Chapter 1).

Admixed populations are precious in elucidating the genetic background of phenotypes, including pathological traits, through the approach of admixture mapping (Leroi, 2005; see Chapter 10).

Toward Homogenization?

These multiple admixture events could lead to the belief that humankind is on the way to thorough homogenization, since human populations are becoming increasingly admixed (Dobzhansky, 1966; Mersha and Abebe, 2015). However, this belief could prove to be only partially true. Indeed, cultural obstacles (language, and most probably racial prejudice) limit gene flow among populations of different ancestries living in sympatry. Since 2000, the US census has abandoned the "one-drop rule" (people had to attribute themselves to only one ancestry). People are allowed to declare two or more ancestries. It is interesting to note that 97.5% of people have declared that they belong to only one race. If mixed marriages were random, the result should have been 42% (Risch et al., 2002). The rate of mixed marriages between European and AFAs in the United States, according to the 2000 census, was 0.3% in European Americans (EURAs) and 4% in AFAs (Ousley et al., 2009). Data are not available for France, since ethnic statistics are against the law in that country. Perhaps cultural obstacles are not the only explanation for the rarity of mixed marriages in the United States. A biological phenomenon of homogamy might play a role. People tend to marry to people who look like them to some extent. It is rare to see very tall men who marry very short women and the opposite is even rarer. Risch et al. (2009) evidenced assortative mating in admixed Mexican and Puerto Rican populations analyzed with 104 AIMs. Correlations were not attributable to variation in socioeconomic status or geographic heterogeneity. So the tendency to look for partners of similar ancestry could have something biological.

Ancestry Informative Markers Versus Self-Reported Ancestry

If one wants to identify the geographical origin of individuals involved in a given study, two approaches are possible: either a genetic identification is performed by using adequate markers or subjects are directly asked from which geographical group they originate.

AIMs are variants whose frequency is very different from one geographical population to another. The use of a carefully selected set of AIMs makes it possible to reliably identify populations of origin as well as degrees of admixture, even at the individual level. AIMs are not "tautological constructs" (Morning, 2014); they are not selected a priori to fit ethnic classifications. They are selected a posteriori after natural groupings have been fully confirmed by randomly selected markers and blind, unsupervised, working hypothesis-free approaches such as with the STRUCTURE model. Lahn and Ebenstein (2009) have noted that the attribution of any individual to one of the major geographic groups was almost 100% reliable with DNA markers. AIMs are very powerful tools to evaluate admixture rates in populations (Pfaff et al., 2001). According to Sarich and Miele (2004), Chapter 1, DNAPrint Genomics (ceased operations in 2009) used to propose a kit of 73 AIMs able to evaluate the percentage of admixture at the individual level. On 3000 blind assays, there was no mistake. Galanter et al. (2012) have designed AIM kits to evaluate contributions of African, European, and Native American ancestries in Latin America. Admixture quantification was reliable for 314, 194, and 88 AIMs, and less reliable with lower numbers. Admixture patterns were variable in the same country, even in the same region. This approach is crucial for association studies of medical traits (see Chapter 10). Parra et al. (2004) measured the correlation between skin pigmentation (estimated with a spectrometer) and level of admixture (estimated by AIMs) in five populations of admixed ancestry. The authors stated that the correlation was quite variable. However, it was constantly high ($p < 10^{-3}$ in four populations out of five, the weakest p being 8×10^{-3}, which still is quite significant). The authors recommended the use of AIMs as the most reliable means for evaluating the degree of admixture.

In conclusion, AIMs are a method of choice to identify the ancestry of a given individual, including in admixed populations. However, their use remains costly and requires a rather high level of expertise. Scientists may prefer to rely on SRA. This is especially adequate in multiracial countries such as the United States (and France), where a limited number of populations with rather dissimilar ancestries live in sympatry. People are offered to identify themselves using the categories of the US census, and can declare several ancestries (no use of the "one-drop rule," which was designed for red tape, not science). It is obvious that genetic markers are preferable (Bustamante et al., 2011), especially in the case of admixed populations such as Hispanics. However the "poor man's method" SRA is better than nothing and is widely used in biomedical research. Risch

et al. (2002) consider it as a very reliable approach. González Burchard et al. (2003) found a fair match between the five continental groups identified by microsatellites and SNPs on the one hand, and SRA on the other. Tang et al. (2005) have compared the results obtained from genetic clustering using 326 microsatellite markers and SRA in 15 localities in the United States and Taiwan. The rate of erroneous attributions by SRA was 0.14% only. Although it has been heavily criticized, especially by social scientists, SRA is considered by many as a useful proxy for biomedical research (Auton et al., 2009; Guha et al., 2012; Li et al., 2008; Mountain and Risch, 2004; Need et al., 2009; Nelson et al., 2012; Novembre et al., 2008; Rosenberg et al., 2002; Shiao et al., 2012).

The Contribution of Ancient DNA: Archaic Adaptative Introgression

The sequencing of ancient DNA is a fearsome technological challenge (Pickrell and Reich, 2014). Although the DNA molecule is extremely stable, old DNAs are degraded. Climate conditions play an important role. Dry, cold climates are favorable for preserving DNA. Moreover, the risk of contamination by modern DNA is high. In spite of these obstacles, advanced laboratories have been able to gather impressive results in the recent years. The present limit is −400,000 years (Pickrell and Reich, 2014).

As we have seen earlier ("All admixed"), ancient DNA was able to elucidate several events of past admixture by comparing DNA from ancient humans with that of contemporary populations. Old debates have been reignited by ancient DNA (Pickrell and Reich, 2014): (1) the origin of the Basques and the Indo-Europeans; (see later in this chapter); (2) "pots versus people": are culture and technology spread by cultural contacts only, or also by physical migrations? (3) demographic stasis (present populations descend directly from ancient populations) versus rapid demographic changes. Against the demographic stasis hypothesis the following cases can be cited: (a) ancient DNA has revealed that Paleosiberians were closer to present-day Native Americans than to present-day Siberians; both modern Europeans and Native Americans may have partly originated from an ancient North Eurasian population; (b) ancient, 4000-year-old inhabitants of Greenland were closer to modern Siberians than to present-day Greenlanders; (c) 5000-year-old Swedish populations showed that Swedish hunter-gatherers of the time were closer to present-day Northern Europeans, while Swedish farmers were closer to modern southern Europeans; and finally, (4) serial founder effect versus replacement/admixture. The serial founder effect is a classic and popular model for retracing human demography: small populations invade a new, empty territory. They grow, then send out new, small groups of emigrants, and so on (Prugnolle et al., 2005). Ancient DNA data seem to favor the replacement/admixture model most (Pickrell and Reich, 2014). The analysis of ancient DNA can yield direct evidence for recent selection, provided that local populations have not been replaced (Wilde et al., 2014; see below: recent evolution).

The analysis of archaic humans' DNA somewhat revolutionized our view on human evolution. Archaic adaptive introgression (AAI; the capture of adaptive genetic variants by modern humans from archaic cousins through occasional crossbreeding) may have provided moderns with many favorable traits, not only for climatic adaptation and resistance to pathogens, but also possibly cognitive properties. This would partly explain the "creative explosion" of the upper Paleolithic in Europe and Asia (Cochran and Harpending, 2009, Chapter 2 and conclusion). Of course this audacious hypothesis about the capture of cognitive traits remains speculative. However, clear indications of AAI for other traits are available. The contribution of archaic genomes to present-day humans would be 1.2−4% Neanderthal in European, Asian, and Native American populations; 3−6% Denisovan in native populations of Papua New Guinea, Australia, and Melanesia; and 0.2% Denisovan in Asian populations (Alves et al., 2012; Novembre and Ramachandran, 2011; Racimo et al., 2015; Stoneking and Krause, 2011). Modern Africans do not show (yet?) any Neanderthal or Denisovan introgression. Apart from introgressions favoring defense against pathogens (see Chapter 10), AAI has been evidenced for: (1) brain genes (see "Brain Genes" in this chapter) and (2) the adaptation of Tibetans to altitude (see "Mountaineers" in this chapter). According to Racimo et al. (2015), AAI is a rich reservoir of new genetic diversity, providing a considerable source of adaptation to new environments. The knowledge of new sequences from archaic humans could help understand the genetic background of phenotypic differences among human populations.

Abundant indication of AAI refutes the hypothesis that Neanderthals did not interbreed with our ancestors (Currat and Escoffier, 2004; Jordan, 2008, Chapter 2).

Old Debates Revisited: Basques, Indo-Europeans, and Jews

Modern population genetics tools and ancient DNA allow us to revisit long-standing historical and linguistic debates dealing with the origin of present and past populations. Many populations have been reexamined this way. We will focus on Basques, Indo-Europeans, and Jews.

Present-day Basques live in Northwest Spain and Southwest France. They are a proud people who feel very

different from their Spanish and French neighbors. They call their country "Euzkadi" in their mysterious language, which does not have an Indo-European origin and is distinct from Spanish and French. They claim that they have a very ancient, common origin. Ancient DNA has recently shed some light on this enigma (Günther et al., 2015). The study dealt with eight individuals from the El Portalón cave in Spain. The age of the individuals ranged from −5500 to −3500 years (from the Chalcolithic to the Bronze era). They have been compared with various present European populations. Unlike other Iberian populations, present-day Basques showed little or no admixture from North Africa and Caucasus/Central Asia and were the closest populations to the eight cavemen. Modern Basques, therefore, are hypothesized to be the direct descendants of early Iberian farmers, and their language, which has no proven relationships with any other language, could be a retention of the preagricultural linguistic diversity in that region.

The cradle of the Indo-European languages is another old enigma. Linguists have long recognized close relationships between most European languages (except Basque and Finno-Hungarian languages), and Indo-Iranian languages. The first debate questions the explanation of this kinship: pots or people (see earlier)? Spread mostly by cultural contacts (Demoule, 2014) or by migrations? If the migration hypothesis is retained, what was the geographical origin of the proto-Indo-Europeans? Two places were candidates: Anatolia and the Russian steppes. Ancient DNA has provided new information to the debate (Haak et al., 2015). Ninety-four ancient Europeans were compared to 2345 present-day individuals within 203 populations. About 400,000 SNPs were used. Modern Europeans are believed to originate from two major migrations: (1) from the Middle East during the early Neolithic era and (2) from the Yamnaya steppe during the recent Neolithic era. This study therefore favors migration rather than cultural contacts only (people rather than pots), and supports the steppe hypothesis rather than the Anatolia hypothesis. However, it does not explain the origin of Indo-Iranian and Southeastern European languages.

The origin of modern Jews has long been discussed. Data from high-resolution genetic markers show that modern Jews share common polymorphisms that help to identify them at the population and, to a certain extent, at the individual level (Cochran et al., 2006; Cochran and Harpending, 2009, Chapter 7; Guha et al., 2012; Need et al., 2009; Novembre and Ramachandran, 2011; Ostrer and Skorecki, 2013). Guha et al. (2012) have focused on Ashkenazi Jews (AJs), who are assumed to be of recent origin (about 1000 years). They characterized 1394 AJs from Israel with 95,600 SNPs (a relatively low number compared to other studies based on up to 1 million SNPs; López Herráez et al., 2009). AJs were compared with populations from Europe, the Middle East, and Central/South Asia. The ADMIXTURE analysis clearly differentiated AJs from the other populations under study. PCA showed that AJs occupied a position between Europe and the Middle East, but with a specific dimension, orthogonal to the two other populations. The authors insisted on the value of AJ population genetics for disease gene mapping (see Chapter 10). Need et al. (2009) considered a random sample of 611 unrelated self-described Caucasian subjects mostly residing in America. The subjects reported themselves whether they were of Jewish ancestry and if so, how many Jewish grandparents they had. Individuals reporting four Jewish grandparents were categorized as full Jewish ancestry (FJA). Most people of Jewish ancestry were AJs. No less than 550,000 SNPs were used. Relationships among populations were visualized using PCA. FJA subjects were clearly separated from non-Jewish individuals. As expected, subjects with one to three Jewish grandparents showed intermediary positions on the PCA representation. On a PCA representation of all the populations studied, Jewish subjects were intermediary between European and Middle Eastern populations. These studies suggest that present-day Jews have kept a notable component of their original Middle Eastern ancestry.

Out-of-Africa and That's It? Not So Simple

We now clearly see the main features of population structure of modern humans at the world level. The dogma for many years has been that this population structure was the result of the so-called OOA hypothesis (Stringer and Andrews, 1988): non-African populations are reportedly the outcome of migrations from East Africa some 100,000 yeas ago, and modern humans would have entirely replaced local archaic hominids. However, little by little, a more complex picture is emerging.

First of all, the OOA ancestry of modern humans some 100,000 years ago (as evaluated by Templeton, 2012; this would instead be −130,000 years) has not been the only one. *Homo erectus* went OOA about 1.3−1.7 million years ago and spread throughout the world (Cavalli Sforza and Feldman, 2003; Templeton, 2012), as far as the Island of Java (the *Pithecanthropus*) and China (the *Sinanthropus*). Then the Acheulean expansion took place some 650,000 years ago (Templeton, 2012).

Moreover, we have seen above that some interbreeding took place between modern humans and their archaic cousins, which seems to have been crucial for the adaptations of OOA emigrants to new environments. The replacement therefore has not been 100% (Templeton, 2012). This is why the OOA has been considered "oversimplified" (Vasseur and Quintana-Murci, 2013). At least two admixture processes have occurred, with Neanderthals (all non-African populations) and with Denisovans (mainly

Oceanian populations) (Alves et al., 2012; Racimo et al., 2015; Stoneking and Krause, 2011). Taking these archaic admixtures into account is very relevant for population genetic analyses. Not doing so leads to overestimating population size and the antiquity of most recent common ancestors. If admixtures are better known, migration patterns will be better evidenced (Alves et al., 2012).

The multiregional model of human evolution (Weidenreich, 1946) proposed a unique OOA some 1.9 million years ago, followed by continuous gene flow among geographically separate populations. Coon (1962) has proposed the candelabra model, in which, following an ancient OOA, different *H. erectus* populations would have separately reached the *Homo sapiens* stage without genetic exchange among them, and would thus be at the origin of major races. Lastly, the OOA replacement model with no archaic admixture was classically the accepted model (Stringer and Andrews, 1988). Nested-clade analysis, which uses information extracted from haplotypes, shows that gene flow has played and continues to play an important role in human evolution, resulting in all modern humans representing a single evolutionary lineage. Moreover, this approach makes it possible to reject the multiregional and candelabra models, and to confirm archaic interbreeding (Templeton, 2012).

The present state-of-the art on OOA might be profoundly modified in the near future by more refined population genetics analyses taking more into account the variability of rare and low-frequency variants, which will give a better estimate of recent and present gene flow in human populations. The analysis of more ancient DNA samples could also reveal unexpected archaic admixtures, such as between Neanderthals and Denisovans (Gibbons, 2015), or maybe between different *H. erectus* populations, or between *H. erectus* and Neanderthals, Denisovans, or *H. sapiens*. It should be recalled that AAI seems to play a major role in human evolution and adaptation. In science, especially in human evolution, never say "it didn't happen" but rather "it has not been evidenced until now." The discovery of *Homo floresiensis* (the "Hobbit") in 2003 (Morwood and van Oosterzee, 2007) shows that prehistoric science can still be upset by new discoveries. Fossil DNA is a fantastic tool. However, (1) until now, few individuals have been conveniently analyzed; (2) fossils are rare and are by no means random samplings of ancient times. The French prehistorian Father Henri Breuil used to say: "the cradle of mankind is a cradle on wheels."

The present-day advances in human population structure might be still much refined. However, it is quite unlikely that the main features will be upset, namely: (1) at least when common historical variants are considered, the genetic diversity within geographical populations is far greater than that between populations; (2) major continental groupings can be evidenced by both phylogenetic and nonphylogenetic (unsupervised, working-hypothesis free) approaches; (3) when enough markers (for example: up to 0.5−1 million SNPs) are used, a highly stratified, Russian doll structure is visible within major continental groupings, at an extremely reduced geographical scale; (4) thorough admixture, but not homogenization, can be evidenced in most present populations. When recent admixture is considered (AFAs, Hispanics), the degree of admixture of populations and individuals can be evaluated by AIMs; (5) AIMs can trace the ancestry of any individual; (6) SRA can be a useful ersatz to identify the ancestry of subjects in multiracial societies.

We now have handy the reliable population genetic framework on which it will be possible to map adaptive, selected genetic, and phenotypic traits (phylogenetic character mapping or PCM; Avise, 2004). Let us now consider some features that are highly relevant for the study of human adaptation.

RARITY MATTERS: RARE VARIANTS AND LOW FREQUENCY VARIANTS

Human population genetics has long relied on common variants, more specifically, neutral, historical markers. CVs tend to be shared among geographical populations, and only some frequency differences make it possible to evidence continental groupings. When phenotypes, and more specifically, disease risks, are considered, the common disease/CV hypothesis states that disease susceptibility was caused by the cumulative action of CVs whose individual penetrance was weak (Keita et al., 2004; see Chapter 10). The massive use of whole genome sequencing, DNA microarrays, and high-resolution markers (for example: up to 1 million SNPs) has upset our view on human genetic variation. CVs are generally defined as having a minor allele frequency (MAF) of $\geq$5%. Low-frequency variants (LFVs) have an MAF ranging from 0.5% to 5% (Goldilocks variants). Rare variants (RV) are below 0.5% (Mersha and Abebe, 2015; Nelson et al., 2012). We speak here about sequence variants. SV will be discussed later. The contribution of RVs and LFVs to relevant traits remains largely unexplored (The UK10K Consortium, 2015).

Crucial features of LFVs and RVs are that they tend to (1) have originated recently, and (2) be localized, and hence population-specific, proportionally to their rarity (Bustamante et al., 2011). Even if the *F*st calculated from CVs is low, LFVs and RVs are able to reliably separate major continental groups (Africa including AFAs, East Asia, Europe, the Americas, including admixed populations). Seventeen percent of LFVs are specific of only one ancestral group. For RVs, the figure is 53% (The 1000 Genomes Project Consortium, 2012). In a survey dealing with 2054 individuals from 26 geographical

populations from Africa, Southeast and South Asia, Europe, and the Americas, analyzed by microarrays and deep sequencing, 88 million variants were evidenced. Most of the variants were rare: 64 million autosomal SNPs were RVs. Only 8 million were CVs. Eighty-six percent of the variants were specific of only one continental group (The 1000 Genomes Project Consortium, 2015).

Another specificity of RVs and LFVs, precisely because they are rare, is that they are most often missed by microarrays and Genome-Wide Association Studies (GWAS). Whole genome sequencing is the best approach to detect RVs and LFVs (Novembre et al., 2008; Rowell et al., 2012).

Lastly, the proportion of deleterious alleles is higher in RVs than in CVs (Henn et al., 2015).

When protein-coding variants are considered, the vast majority of them are rare, and indeed enriched with deleterious alleles. These rare protein-coding variants are probably highly relevant for the study of phenotypes and diseases (Belizário, 2013). According to Casals and Bertranpetit (2012), the demographic explosion linked to the advent of agriculture 10,000 years ago, has yielded a vast excess of RVs compared to the expectations of classical population genetics, many of them being possibly deleterious. This would be due to the impossibility of natural selection to eliminate the deleterious mutations in too short a time, and could affect the fitness of future generations. The authors have estimated that 70−90% of RVs were continent-specific, while 20−30% were specific of populations within continents.

Fu et al. (2013) studied 4298 EURAs and 2217 AFAs by resequencing 15,336 genes. In agreement with the hypothesis postulated by Casals and Bertranpetit (2012), they have inferred a huge excess of rare variants. By coalescence simulations, the authors have estimated that 86.4% of the single-nucleotide variants (SNVs) had arisen in the past 5000 years (91.2% and 77.0% for EURAs and AFAs, respectively). This recent demographic explosion would have resulted in a deluge of rare functionally important variation, with a larger burden of Mendelian disorders, but also a new reservoir of advantageous alleles (Hawks et al., 2007).

Tennessen et al. (2012) performed exome sequencing on 1351 EURAs and 1088 AFAs identified by AIMs. They have found 86% of RVs, of which 82% were unknown, and 52% were restricted to either EURAs or AFAs. According to the authors, RVs and LFVs would explain the heritability of common complex diseases (see Chapter 10), while CVs would be responsible for only a modest fraction of the heritability of most phenotypic traits. In agreement with the results by Casals and Bertranpetit (2012) and Fu et al. (2013), the authors have found a great excess of RVs, suggesting a recent demographic explosion about 5000 years ago. The vast majority of the coding variation appears to be recent, rare, and enriched with deleterious alleles. These features are most relevant for phenotypic variation and disease susceptibility. Since most RVs are population-specific, association studies among different populations are challenging.

In summary, LFVs, and even more, RVs, tend to be population-specific and of recent origin, as a result of a recent demographic explosion. They seem to play a much greater role than CVs in phenotypic and disease susceptibility diversity.

COPY NUMBER MATTERS: STRUCTURAL VARIATION

One major discovery of modern genomics has been to show that human populations exhibit a high variability of structural variants—that is to say, segments of the genome that have one, two, or more copies, or have different orientations among individuals and populations. According to Conrad and Hurles (2007), all of population genetics science should be revisited in light of SV. The database of genomic variants (http://dgv.tcag.ca/dgv/app/hom) has cataloged more than 100,000 CNVs (Belizário, 2013).

SV is observed in healthy individuals (Conrad and Hurles, 2007; Lander, 2011). It comprises: (1) CNVs, which can be diallelic or multiallelic, and involve deletions and duplications; (2) inversions and balanced translocations. The former changes the DNA dosage, the latter do not. SV ranges from 1 kilobase (kb) to more than 3 megabases (Mb) (Conrad and Hurles, 2007). CNVs are considered to play a more important role in phenotypic variation and human adaptation than SNVs (Belizário, 2013; Fu and Akey, 2013; Gonzaga-Jauregui et al., 2012; Vasseur and Quintana-Murci, 2013), and "SVs seem to have a disproportionate impact on gene expression relative to their number" (Sudmant et al., 2015b). SV affects more base pair (bp) polymorphisms than do SNPs outside SV (Sudmant et al., 2015b). According to Sudmant et al. (2015a), 7.01% of the human genome is variable because of CNVs, while SNVs are the cause of 1.1% of this variability only. About 2100−2500 SVs affect 20 million nucleotide bp (The 1000 Genomes Project Consortium, 2015).

SVs are observed in healthy subjects. However, they are involved in various pathologies (see Chapter 10).

Lastly, as we have already shown (see "A Mankind Population Genetics Framework for Applied Research"), SV varies among populations and corroborates continental groupings evidenced by microsatellites, SNPs, and other genetic markers (Jakobsson et al., 2008; Sudmant et al., 2010). As is the case for genic RVs, rare SVs tend to be specific of continental groupings (Sudmant et al., 2015b)

NOT ONLY GENES: REGULATION IS A MAJOR ACTOR

Gene regulation is considered to have a major role in evolution. King and Wilson (1975) have hypothesized that biological differences between humans and chimpanzees were better explained by regulatory mutations than by sequence differences. Indeed, the sequences of the two species present a high similarity (98.77%; Chimpanzee Sequencing and Analysis Consortium, 2005). This hypothesis has been recently supported by Fu and Akey (2013), who have stated that differences in gene expression between humans and chimpanzees were considerable, particularly at the level of the brain.

Belizário (2013) has underlined the relevance of studies dealing with delineation of genome-wide DNA methylation patterns (epigenome) and full characterization of coding and noncoding RNAs (transcriptome), together with classical genome sequencing approaches, to better elucidate the mechanisms of phenotype and disease risk diversity. The author has noted that 90% of the SNPs associated with human phenotypes are not in protein-coding regions. According to Enard et al. (2015), Fraser (2013), Grossman et al. (2013), Lander (2011), and Stranger et al. (2007), regulatory changes and gene expression have been more important than amino acid substitutions in the evolution and local adaptation of human populations. Fu and Akey (2013) have proposed that regulatory, soft, polygenic, epistatic adaptation was more important than hard adaptive events ("hard sweeps": see "Abundant Indications for Recent and Geographically Differentiated Evolution"), in human evolution, a view shared by Karlsson et al. (2014). Spielman et al. (2007) compared gene expression of transformed lymphoblastic cells in three populations of the HapMap project: 60 CEU (EURAs), 41 Han Chinese (CHB), 41 Japanese (JPT), and 24 Han Chinese from Los Angeles (CHLA). Differences were highly significant at a statistical level of $p < 10^{-5}$ between groups of European versus Asian ancestry. Differences involved 1097 out of 4197 genes. The highest difference was for the *UGT2B17* gene (which codes for an enzyme), ie, expression in the CEU group was 22 times higher than in the CHB + JPT samples. Heyn et al. (2013) have analyzed whole genome DNA methylation profiles of β-lymphocyte cells in 96 AFAs, 96 EURAs, and 96 Asian Americans (ASAs; Han Chinese). They found that DNA methylation profiles clearly separated the three populations (Fig. 6.5).

One-third of the DNA methylation variation was not related to any genetic modifications: variation in population-specific sites would be explained by both the genetic and epigenetic modifications, underlining the relevance of epigenetic activity in human variation. The results suggested a regulatory network that contributes to the variance observed between populations. Martin et al. (2014) have sequenced the genomes, exomes, and transcriptomes of Epstein–Barr virus transformed lymphoblastoid cell lines derived from 45 individuals of diversified geographical origins (HGDP; Namibian San, Mbuti Pygmies of Congo, Mozabites, Pathan of Pakistan, Cambodians, Yakut, and Mayans of Mexico). They found that about 25% of the variation in gene expression could be attributed to population differences. However, few genes were systematically differentially expressed among populations. Lastly, Sudmant et al. (2015b) have noted that SV seemed to have "a disproportionate impact on gene expression relative to their number."

The data above show that (1) gene regulation is probably more important than amino acid changes in human evolution and adaptation. Consequently, whole exome sequencing, which concerns only the coding part of the genome, is not relevant to capture this key feature of human adaptation (Manry and Quintana-Murci, 2013). (2) Populations of different geographical origins exhibit different patterns of gene regulation, probably related to local adaptation and different selective pressures.

WHAT ABOUT PHENOTYPIC GEOGRAPHICAL VARIATION?

We have shown in this chapter that there is a clear association between: (1) diversity of genes, gene regulation, and SV on one hand and (2) geographic origin on the other hand. What about phenotypic variation? Everyday experience suggests that to a large extent it is possible to guess the geographic origin of individuals according to their external aspect. This is largely due to the fact that phenotypic traits are not independent of each other, but show clear correlations. People of African ancestry not only have darker skin than Europeans but they also never have blue eyes. Blue eyes are more frequent in blond individuals. Slanting (never blue) eyes in people of Asian ancestry are generally associated with dark, thick, coarse hair. But everyday experience is not enough for scientific conclusions. What about data?

According to Relethford (2009), the heritability of skin color is 0.66. Harpending (2002) noted that the *F*st (which shows the differences between populations) applied to skin color ranged from 0.60 to 0.90, a far higher figure than the *F*st inferred from common genetic variation (0.05–0.15). Relethford (2009) found *F*st = 0.88 for skin color between the five main geographical regions and noted that there were no major discontinuities in skin darkness among human populations. Both strong *F*st and progressive variations are hardly astonishing: color reflects climatic adaptation (Relethford, 2009) and is correlated with UV

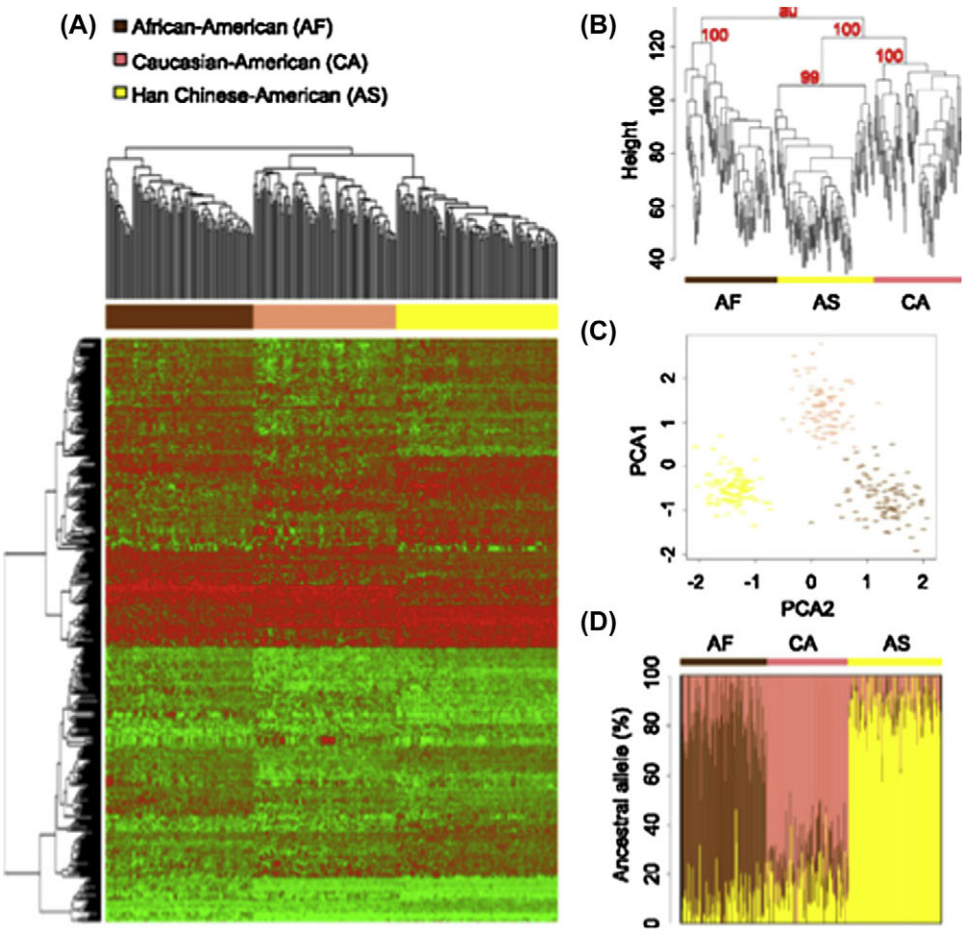

FIGURE 6.5 DNA methylation (involved in gene regulation) separates African-American (AF, *brown*), Caucasian-American (CA, *pink*), and Han Chinese-American (AS, *yellow*) individuals. (A) Hierarchical clustering of 439 differentially methylated DNA sites separating the three populations using absolute DNA methylation levels (low: green; high: red). (B) Multiscale bootstrap resampling ($n = 10{,}000$) of the 439 DNA sites significantly differentially methylated between African, Asian, and Caucasian individuals. The three populations cluster separately and consistently with prior genetically defined proximities. (C) Principal component analysis (PCA) of the differentially methylated DNA sites. (D) ADMIXTURE analysis of these patterns of differential methylation. Each individual is represented by a vertical line, with the lengths corresponding to the ancestry coefficients in up to three inferred ancestral groups (Heyn et al., 2013).

radiation (although Harpending (2002) proposed that sexual selection plays a role as well). Let us recall here that Parra et al. (2004) have found a significant correlation between skin color and admixture level evaluated by AIMs, which shows that this phenotype is related to general genetic polymorphism, since AIMs have no role in skin color.

Sarich and Miele (2004; the race affair) emphasized that morphological variation (skull and face among continental populations, ie, "races") was 10 times stronger than between genders in the same continental group, and higher than the morphological differences between chimpanzees and bonobos, two different species of apes. Unfortunately, their book lacks precise scientific references.

More reliable data come from tooth and skull studies. Edgar (2009) has compared dental morphology (assumed to be neutral and heritable) in 1445 subjects (EURAs and AFAs) and their ancestors since the 17th century. According to the author, Europeans of different origins (west, south, east) were fairly admixed (in spite of the fact that Southern and Eastern Europeans were long discriminated against in the United States), while admixture obtained much less between EURAs and AFAs. This study shows that biological distances inferred from dental morphology can distinguish Europeans from different origins, and EURAs from AFAs. Moreover, it suggests that cultural obstacles still limit interbreeding between EURAs and AFAs today, although biological homogamy could play a role too (see "Toward Homogenization?"). Studying 4666 male skulls from various populations, plus a more limited sample of female skulls, Manica et al. (2007) found that the loss of genetic diversity having followed the OOA

was correlated with a loss of phenotypic diversity (after correction for the climatic impact).

Ousley et al. (2009) noted that craniometric variation worldwide showed strong geographic patterning, but also differences among populations from the same continent. Their results show that individuals can be accurately classified into geographic origin using skull measurements, although different groups overlap. When the number of measurements increased, the discrimination was clarified, which shows that different traits are correlated: this calls for multivariate methods. Multivariate analysis confirmed that AFAs and EURAs could be distinguished by craniometrics.

Relethfod (2009) confirmed that craniometric data were able to assign individuals to their geographic origin. A cluster analysis built from the craniometric distance matrix showed a clear separation between the six geographic regions covered by the sample (Polynesia, Australasia, East Asia, the Americas, Europe, and sub-Saharan Africa). This pattern is similar to the one observed with genetic markers (see Figs 6.1−6.4) and with gene regulation diversity (Fig. 6.5). However, the author observed that this collection was not randomly sampled and was based on regions far away from each other. Moreover, like Ousley et al. (2009), Relethford (2009) has found that craniometric measures exhibited an overlap between different geographical populations.

Two classical morphometric studies have been revisited using modern statistical tools. Sparks and Jantz (2002) reexamined an important part of the skulls studied by Boas (1912) with modern statistics. They claimed that the main hypothesis by Boas (that cranial morphology variation is weakly heritable and mostly explainable by environmental parameters) was wrong. According to the authors, genetics plays a stronger role than environment in skull morphology. Moreover, they have observed that cranial morphology of AFAs and EURAs evolved, but did not converge, which would be expected if environment had a major impact. Another revisited classical study dealt with the results produced by Morton (1849) on cranial comparisons between AFAs and EURAs. These results had been severely criticized by Gould (1981). However, Lewis et al. (2011) have reexamined both studies and have directly remeasured almost 50% of the approximately 1000 skulls studied by Morton (while Gould had only checked Morton's measurements). Lewis et al.'s conclusion was that only 2% of the results by Morton were wrong, and therefore, that Gould's criticism was not justified. AFAs and EURAs did show significant differences in cranial measurements, which confirm the results by Sparks and Jantz (2002).

In summary, skin color as well as dental and cranial morphology are heritable and exhibit strong geographical diversity. Skin color and cranial morphology do not show discrete variation, but rather change progressively among populations. Both dental and cranial morphology can be used to reliably identify the geographical origin of the individuals under study, as do genetic markers.

ABUNDANT INDICATIONS FOR RECENT AND GEOGRAPHICALLY DIFFERENTIATED EVOLUTION

Two recent books of scientific popularization (Cochran and Harpending, 2009; Wade, 2014) have supported roughly the same hypothesis: that evolution has not stopped with the advent of modern humans 40,000−50,000 years ago, as was widely believed (Mayr, 1963; Lawler, 1978; Gould, 2000), but on the contrary, it (1) sped up in non-African populations through admixture with archaic humans; (2) exploded with the Neolithic revolution and the advent of agriculture; and (3) was abundant, local, and geographically diversified (Hawk et al., 2007). Cochran and Harpending (2009), Chapter 1 hypothesized that present-day humans have very different minds and bodies from those of people only a few 1000 years ago. Differently from Sarich and Miele (2004), the books by Cochran and Harpending and by Wade cite abundant sources of references. Some of the hypotheses proposed by these authors, in particular those dealing with cognitive evolution, and correlations between genetically driven cognition and the economic success of societies, remain speculative. However, many of the data they present are corroborated by recent scientific studies. Lahn and Ebenstein (2009) and Stearns et al. (2010) share the view that human evolution has not stopped and still is going on.

As a start, it should be noted that evolution and natural selection are obviously operating in the present before our very eyes if we consider transmissible diseases (Tibayrenc, 2004, 2007a,b). One example among many others, Malaria, kills an incredible number of infants every year, especially in sub-Saharan Africa. It would be unexpected that natural selection did not favor the genetic background of the survivors. This point will be developed in Chapter 10.

A few reminders will help understand this part on selection/adaptation. Evolutionists distinguish several types of selection. (1) Purging selection is the most common mode of selection, and concerns the elimination of deleterious alleles. If alleles are only mildly deleterious, their elimination can take a long time. In this case, many alleles will exhibit intermediary frequencies, because they are on the way to being eliminated and the process continues. (2) Darwinian = directional = positive selection deals with the selection of favorable alleles that augment the fitness of the organism. Again, if the allele is only slightly favorable, its fixation (frequency = 1) will be slow, and mildly favorable alleles will often exhibit intermediary frequencies. (3) Balanced selection occurs when the

advantage of the allele is frequency-dependent, or when the heterozygous state is favored, while the homozygous states are not. Sickle cell anemia is a classical case of balanced selection. Heterozygous individuals are protected against malaria, while subjects who are homozygous for the sickle cell anemia trait undergo a high mortality rate (see Chapter 10). In principle, adequate statistics dealing with genomic patterns can distinguish between the different kinds of selection, and their respective strength (Cavalli-Sforza and Feldman, 2003; Colonna et al., 2014; Enard et al., 2015; Fu and Akey, 2013; Fumagalli et al., 2015; Lachance and Tishkoff, 2013; Pritchard et al., 2009; Shriver et al., 2004; Tennessen and Akey, 2011; Vasseur and Quintana-Murci, 2013). Lastly, it is important to emphasize the fact that selection acts on global phenotypes rather than directly on genotypes (Stearns et al., 2010).

"Selective sweeps" designate the changes of allele frequencies due to selection events. The most classical kind is the "hard sweep," in which strong selection drives new mutations quickly to fixation in given populations. "Soft sweeps" use existing (standing) variation and select alleles that are moderately favorable, or alleles that are roughly equally favorable at the same locus. The genomic signature of hard sweeps is much stronger than that of soft sweeps (Pritchard et al., 2009). Convergent evidence suggests that recent human adaptation relies little on hard sweeps and much more on soft sweeps of multiple genes, regulatory, and epistatic phenomena (Alves et al., 2012; Daub et al., 2013; Fu and Akey, 2013; Karlsson et al., 2014; Tennessen and Akey, 2011; Wade, 2014, Chapter 1). Soft selection operates on standing variation and is therefore comparable to artificial selection on domesticated plants and animals.

Everything that has been said above on RVs/LFVs, rare CNVs, and geographically localized genetic regulation is highly relevant to human recent evolution. As stated above, RVs/LFVs tend to be restricted to geographical groups, including at a small scale. Moreover, they are considered to play a major role (greater than that of CVs) in phenotypic diversity, adaptation, and disease risk, as do CNVs and regulatory mechanisms. Some remarkable examples of recent adaptation will be exposed in the next sections.

Mountaineers

Some human groups live at high altitudes; this is the case for Tibetans, Native Americans of the Altiplano in Andean countries (Aymaras), and the Ethiopians of the Highlands. The three groups show a remarkable adaptation to altitude, although through different mechanisms. The oxygen saturation profile of Ethiopian highlanders is different from that of Aymaras and Tibetans (Lachance and Tishkoff, 2013). Tibetans exhibit specific mutations in the *EPAS1* gene that are associated with hypoxia, and are reported to come from a Denisovan archaic introgression (Racimo et al., 2015). According to Fu and Akey (2013), *EPAS1* patterns in Tibetans corresponds to a hard sweep. The frequency difference with Han Chinese is considerable. Aymaras do not have *EPAS1* mutations but they do have selection signals related to altitude in the *PRKAA1* and *NOS2A* genes, which Tibetans do not have. Both Tibetans and Aymaras have altitude-related selection signals in the *EGLN1* gene (Vasseur and Quintana-Murci, 2013). Aymaras have a striking morphological and physiological adaptation to altitude. I know these people well, having spent more than 7 years in Bolivia. They have a barrel-shaped chest allowing a greater respiratory capacity, and show physiological polyglobulia (see Fig. 6.6). Long-term studies of the Bolivian Institute of Altitude Physiology (Instituto Boliviano de Biologica de Altura, IBBA; http://saludpublica.bvsp.org.bo/ibba/), supported by French cooperation, have shown that the adaptation to altitude was optimal for Aymaras, who are the most anciently established people on the Altiplano. Adaptation is less good for Quechuas, who are the descendants of the Incas, and have been there for a few 100 years only. (The few) Bolivians of European ancestry exhibit the worst adaptation to altitude. Even individuals born in La Paz may suffer from pathological polyglobulia and may have to live in the lowlands. Admixed people (the case of many Bolivians) are halfway between people of European ancestry and Native American Bolivians.

White-Skinned, Blue-Eyed

A classical explanation for light skin adaptive value is the necessity to absorb more UV and synthesize more pro-vitamin D in climates with low UV radiation (Cochran and Harpending, 2009, Chapter 3; Vasseur and Quintana-Murci, 2013). According to Wilde et al. (2014), Neolithic diet changes would have played an indirect

FIGURE 6.6 This Aymara woman and her child show typical "Altiplano faces" with red cheeks, indicating a physiological polyglobulia. This is an adaptation to the low oxygen level that exists at 4000 m.

selective role. Preagricultural societies enjoyed a meat and fish, vitamin D−rich diet, in particular through the consumption of fish livers. The agricultural diet was far less vitamin D rich, and therefore led to a selective pressure for light skin. In Europe, the *SLC24A5* and *SLC45A2* variants are considered to be responsible for light skin (Cochran and Harpending, 2009, Chapter 1; Colonna et al., 2014; Lachance and Tishkoff, 2013). The *SLC24A5* variant has a strong selective advantage. It seems to have spread throughout Europe in 5800 years (Cochran and Harpending, 2009, Chapter 4). It is present in approximately 100% of Europeans, and is nearly absent in people of African and East Asian ancestry (Lahn and Ebenstein, 2009). The *SLC24A2* and *SLC24A5* variants are not the only ones involved in light skinning. Analyzing ancient DNA from Ukrainian individuals of early Neolithic and Bronze Age eras, and by comparing them with that of modern Ukrainians, Wilde et al. (2014) have found direct evidence for selection, not only for *SLC24A2*, but also for two other genes involved in pigmentation pathways, namely *HERC2* and *TYR*. An SNP in the *BNC2* gene is associated with skin pigmentation and freckling in Europeans, in whom a Neanderthal archaic variant of this gene has a frequency of 0.70, while it is absent in Asia and Africa (Racimo et al., 2015). According to Novembre and Han (2012), comparable selective pressure (low UV radiation) has led to different genetic responses leading to light skin in different geographical areas, therefore constituting a case of convergent evolution (Cochran and Harpending, 2009, Chapter 4; Jablonski and Chaplin, 2012; Wade, 2014, Chapter 4). The *MC1R* variant responsible for light skin is found in East Eurasia and the Americas only, while the *SLC24A5* variant is restricted to Western Eurasia, namely Europe, the Middle East, and Central Asia (Pickrell et al., 2009), and the *KITLG* variant is observed throughout Eurasia and the Americas (Novembre and Han, 2012). An *ABCA12* variant is reported to be involved in adaptation to low UV radiation as well. Its derived allele frequency is 0.96 in Asia, 0.91 in Europe, and 0.13 in Africa (Colonna et al., 2014). *OCA2*, *MYO5A*, *DTNBP1*, and *TYRP1* are four genes involved in skin pigmentation. They show clear evidence of selection in Europeans (Voight et al., 2006). *OCA2* and *TYRP1* both show very different frequencies between Europe and Central Asia (Pickrell et al., 2009).

Some genetic backgrounds that could play a role in skin color still have to be identified; Grossman et al. (2013) have uncovered various genes involved in biological pathways, including skin pigmentation, thought to have undergone recent selection. Quantitative trait loci (QTLs) are loci harboring genes that command quantitative traits such as skin color. Quantitative phenotypes have a polygenic command. The role of these QTLs in skin-color variance remains poorly known (Gonzaga-Jauregui et al., 2012). Lastly, gene regulation appears to play a role in skin pigmentation; Fraser (2013) has inferred that regulatory phenomena were involved in adaptation to UV radiation. Vernot et al. (2012) have found enrichment in regulatory noncoding regions involved in melanogenesis in Europeans.

The *OCA2* gene pertains to the melanin pathway (melanin is the pigment that makes the skin more or less dark). This gene is involved in skin pigmentation (Pickrell et al., 2009; Voight et al., 2006), and is also responsible for blue eyes, through a regulatory mechanism operated by the neighbor gene *HERC2* (Colonna et al., 2014). The variant concerned is more frequent in Northern Europe and is centered on the Baltic Sea (Cochran and Harpending, 2009, Chapters 4 and 5).

Milk Drinkers

In most populations of the world, only babies are able to drink and properly digest milk, thanks to an enzyme called lactase, allowing them to digest the lactose (the sugar found in the milk). After babyhood, the lactase gene is repressed, except in a few human groups. Lactase persistence is a now-classical example of recent human adaptation due to a specific diet. It is observed in human groups who rely on milk feeding: Europeans (more in the north), some East Africans, and the Fulani in West Africa. In Europe, a mutation in the promoter (the DNA region that initiates transcription of a given gene) of the lactase gene is responsible for lactase persistence. In East Africans, a different mutation is involved (Vasseur and Quintana-Murci, 2013). This is a case of convergent evolution. In the Fulani, the European polymorphism responsible for lactase persistence has a frequency of 0.37. It has been hypothesized (Arama et al., 2015) that lactase persistence played a role in the specific malaria resistance observed in the Fulani (see Chapter 10). Mathieson et al. (2015) analyzed 230 ancient West Eurasians DNAs (−6500 to −1000 years) and found that the earliest appearance of the variant responsible for lactase persistence was −2200 or −2300 years old. According to Cochran and Harpending (2009), Chapter 3, this variant was absent 7000 years ago. These authors (Chapter 6) have hypothesized that lactase persistence had given a strong selective advantage to the Indo-Europeans, since dairy farming produces five times more calories per hectare than fleshing.

Other Examples of Recent Evolution

Since the advent of agriculture, bones have become slighter. Brow ridges have disappeared, except in Australian natives. UK skull morphology has changed a great deal over the past few 100 years (Cochran and Harpending, 2009, Chapter 4). A decrease in long bone

strength since the upper Paleolithic has been confirmed by Ruff et al. (2015). Analyzing ancient DNA from West Eurasians, Mathieson et al. (2015) found indications for selection at loci dealing with diet, height, tooth morphology, and hair thickness. For most of the selection signals detected, allele frequencies of present Europeans were outside the range of any ancient populations, suggesting that phenotypically, Europeans of 4000 years ago were different in important respects from Europeans today despite having overall similar ancestry. This corroborates Cochran & Harpending's view (2009), Chapter 1. The Inuits exhibit a remarkable adaptation to cold climates and a marine diet (Tishkoff, 2015). Lastly, according to Wade (2014), Chapter 1, the age of first reproduction is tending to decrease, while the contrary is true for the age of menopause.

Coevolution Between Culture and Genetics

Cochran and Harpending (2009; conclusion) emphasized the importance of coevolution between culture and biology. The "niche construction theory" states that organisms modify their environment, which in turn has an impact on their evolution (Laland et al., 2010). Richerson et al. (2010) have proposed that cultural evolution was the leader rather than the lagger of biological evolution. The "Baldwin effect" states that learned behaviors have an impact on evolution and selection. This could have been very important in human evolution. Lactase persistence in dairy-producer human groups is a remarkable example of this.

Brain Genes and Cognition

This is obviously a touchy subject. I will stick to a few rough observations and examples. Ethical aspects on human population differences will be more developed in Chapter 38. Richardson (2011) noted that before the present postgenomic era, supporters of racial IQ differences have never been able to prove that culture and education did not have a major impact on intelligence/IQ (see Arvey et al., 1994; Rushton and Jensen, 2006). Postgenomics might change the game. Research on recent positive selection on brain genes has "potentially explosive implications" (Richardson, 2011). Many scientists are of the opinion that positive selection on cognitive genes has acted differently on populations after OOA and that people of different ancestries could have different intellectual strengths (Richardson, 2011). However, until further notice, no clear relation between brain genes and intelligence has been established. Now some relevant observations on brain genes have been made. Ayub et al. (2013) looked for positive selection in target genes of the transcription factor *FOXP2*, involved in language and language disorders. They have found clear evidence for positive selection in *FOXP2* target genes in Europeans, not in Asians and Africans. *FOXP2* is the result of a selective sweep in modern humans. It is shared between them and Neanderthals. It would come either from a Neanderthal AAI, or from the common ancestor between Neanderthals and modern humans (Cochran and Harpending, 2009, Chapter 2; Krause et al., 2007). The brain growth and development-related genes *ASPM* and microcephalin 1 (*MCPH1*) exhibit signs of natural selection and a clear geographic structure, correlated to linguistic tone variation (Laland et al., 2010). Mekel-Bobrov et al. (2005) observed that a variant of the *ASPM* gene, having arisen about 5800 years ago, was clearly more frequent in Europe and the Middle East than in other regions, due to recent positive selection. The authors inferred that the human brain was still undergoing adaptive evolution. The *ASPM* and *MCPH1* genes have been the theme of intense debates some years ago. Evans et al. (2005, 2006) proposed that the *MCHP1* Haplogroup D, which is hypothesized to be the outcome of an AAI (possibly from Neanderthal; Wolpoff, 2009), and arose approximately 37,000 years ago (at the time of the advent of modern human behavior such as art and the use of symbolism), had undergone strong natural selection, possibly associated with brain phenotypes, and had radically different frequencies among geographical populations. These conclusions were challenged by Richardson (2011), who observed that (1) these variants show no correlation with either brain size or IQ; and (2) they are expressed in various tissues, not the brain only. However, the debate on *ASPM*, *MCPH1*, and cognition still goes on. It has been proposed that microcephalin was not associated with IQ at the individual level, but exhibited a strong correlation with IQ at the population level (59 populations compared; Woodley et al., 2014).

As a last example of recent evolution of cognition, Cochran et al. (2006) presented an audacious and fascinating hypothesis to explain the high level of intelligence in AJs. As we have seen, this community is assumed to have a recent origin (about 1000 years ago), and has maintained strong endogamy for religious reasons and because of persecutions. In Medieval Europe, AJs specialized in money trade jobs, which require high mental abilities. The better they were at the job, the richer they became, and the more children they had. This with endogamy gave the classical conditions for accelerated natural selection. According to the authors, AJs have paid a heavy price for their increased IQ. Selection would have acted on genes that boosted IQ at a heterozygous state, but provoked severe disorders (such as Tay-Sacks disease, very frequent in AJs) at a homozygous state.

It is most probable that cognition and behavioral traits have a polygenic basis and that environment and education play a major role in their expression (Jordan, 2008, Chapter 4; Jorde and Wooding, 2004; Zietsch et al., 2015), which

makes the study of cognitive traits a challenge. However the progress of genomics should make it possible to clarify the genetic background of psychological traits and of their possible variations among geographical populations.

It can therefore be concluded that as a whole, Cochran and Harpending's (2009) and Wade's (2014) hypothesis that clear signs of recent (and possibly present) and geographically differentiated evolution exist, for many traits, including diet adaptation, morphological features, and brain adaptation. Evidence for recent selection on pathological traits will be presented in Chapter 10. However, the data should be interpreted with caution, since this field is subject to much storytelling (the Panglossian paradigm; Gould and Lewontin, 1979). It is safe to infer that lactase persistence has been selected by the special diet of diary-feeding populations. It is very tentative to infer that isolated genetic data will make it possible to understand macrohistorical features. For example, it has been proposed that wealth differences among geographical populations could be explainable by the level of genetic diversity (expected heterozygosity), which would be optimal in Europeans and Asians, excessive in Africans, and insufficient in Native Americans (Ashraf and Galor, 2011; Conley et al., 2014). In turn, there is no proof of a total lack of influence of human biological diversity on history and civilizations, as claimed by Levy-Strauss (1952).

CONCLUSION

We are only at the beginning of the wave. Exponential technological progress in genomics, postgenomics, data computation, and the concomitant drastic decrease of their costs will soon make population genomics and personalized medicine (see Chapter 10) a routine affair. Our knowledge on the human population structure has already reached an unbelievable level of refinement. Many data have been gathered on indications of recent selection in human populations. However, strong challenges remain. The fact that rare and very rare variants seem to play a major role in human evolution explains much of the still ongoing "missing heritability" (Lander, 2011; Nelson et al., 2012), since by nature, these variants are extremely difficult to detect and make that GWAS requires huge sample sizes. The role of regulation, epistasis, interaction between alleles of the same gene and between different genes, and CNV still lacks sufficient knowledge. Last but not least, exploring the interaction between biological evolution and environmental/cultural factors is the new frontier of our knowledge on human nature. Many authors have pleaded for integrative and holistic strategies able to cross this frontier (see, for example, Cochran and Harpending, 2009, conclusion; Vasseur and Quintana-Murci, 2013). The very design of the present book, with its balance between various social and biological disciplines, reflects the thought that human nature can be explored only by thorough multidisciplinary approaches.

GLOSSARY OF SPECIALIZED TERMS

Allopatry Living in different geographic locations (see sympatry).

***Alu* insertion sequence** Dispersed repeated DNA sequences in the human genome, consisting of roughly 300 bp in approximately $3-5 \times 10^5$ copies, constituting roughly 5% of the human genome. These sequences are easily transposable. They are specifically cleaved by the restriction enzyme *Alu* I.

Amplification fragment length polymorphism (AFLP) Selective amplification of genomic restriction fragments (obtained by RFLP) by PCR.

Autosomal Designates all chromosomes, but sexual chromosomes.

Clade Evolutionary lineage defined by cladistic analysis. A clade is monophyletic (it has only one ancestor) and is genetically isolated (it evolves independently) from other clades.

Cladistic analysis A specific method of phylogenetic analysis designed by the German entomologist Willy Hennig (1966). It is based on the polarization of characters that are separated into ancestral (plesiomorphic) and derived (apomorphic) characters. Only those apomorphic characters that are shared by all members of a given clade (synapomorphic character) are considered to be phylogenetically informative. For example, feathers are specific of the clade "birds" (which is a class) and are featured by all birds. They are synapomorphic characteristics of that clade.

Coalescence time Time elapsed between the common ancestral copy (one gene in one individual) and two or more copies of a given gene at the present time.

Copy-number variant (CNV) DNA sequence $\geq$1 kb, present with a variable copy number by comparison with a reference genome. Includes insertions, deletions, and duplications.

DNA microarray (=DNA chip) A set of microscopic DNA spots attached on a solid surface. DNA microarrays are used to measure the expression levels of large numbers of genes simultaneously or to genotype various genomic regions. Each DNA spot (=probe) contains picomoles ($=10^{-12}$ mol) of a specific DNA sequence.

Epigenetics Deals with the activation and deactivation of genes without any change in the corresponding DNA sequence of the organism.

Epistasis Occurs when the expression of one gene is affected by the expression of one or more independently inherited genes.

Exome The coding part of the genome (no more than 1–2% of the total human genome).

Fitness The relative ability of an organism to survive and to transmit its genes to the next generation.

Genome-wide Association study (GWAS) Compares the repartition of DNA markers across the genome (either microsatellites or SNPs) in people with a disease or other phenotypic traits to people without the disease or traits. The goal is to identify the genomic region where the genes responsible for the traits under study is localized.

Heritability Proportion of variation in a trait among individuals in a population that can be attributed to genetic effects.

Heterozygote, heterozygous In a diploid organism (each chromosome has two copies, one comes from the male, one comes from the female), the two copies of a given gene in one individual have

a different molecular structure: this individual harbors two different alleles of the same gene.

Homozygote, homozygous In a diploid organism, the two copies of a given gene in one individual have identical molecular structures.

Homoplasy Possession in common by distinct phylogenetic lineages of identical characters that do not originate from common ancestry. The origin of homoplastic characters include the following: (1) convergence (possession of identical characters derived from different ancestral characters, due to convergent evolutionary pressure, for example, the wings of birds on one hand and of bats on the other hand); (2) parallelism (possession of identical characters derived from a single ancestral character, and generated independently in different phylogenetic lineages); and (3) reversion (restoration of an ancestral character from a derived character).

Isoenzymes Protein extracts of the biological samples under analysis are separated by electrophoresis. The gel is then processed with a histochemical reaction involving the specific substrate of a given enzyme. This enzyme's zone of activity is then specifically stained on the gel. From one sample to another, migration differences can be visible for this same enzyme. These different electrophoretic forms of a given enzyme are referred to as isoenzymes or isozymes. When given isoenzymes are driven by different alleles of a single gene, they are more specifically referred to as alloenzymes or allozymes. Differences in migration result from different overall electrical charges between isoenzymes. Overall electric charges are a resultant of the individual electric charges of each amino acid (AA) of a given enzyme. The AA sequence is the direct result of the DNA sequence of the gene that codes for this enzyme. It is therefore considered (and verified) that isoenzyme polymorphism is a faithful reflection of the genetic polymorphism of the organism under study.

Microsatellite A short DNA sequence, usually 1−4 bp long, which is repeated together in a row along the DNA molecule. In humans, as in many other species, there is great variation from one person to another (widely used in forensic applications for individual identification) and among different populations in the number of repeats. Numbers of repeats for a given locus define microsatellite alleles. There are hundreds of places in human DNA and in most other species that contain microsatellites.

Penetrance The extent to which a given gene is expressed in the phenotype of the individuals who carry it.

Phenotype All observable characteristics of a given individual or a given population distinct from the genome. The phenotype is not limited to morphological characteristics and includes, for example, physiological parameters (blood pressure, muscular strength, etc.) biochemical parameters (level of cholesterol, etc.), or cognitive properties. The phenotype is produced by the interaction between genotype and the environment. The variable part that is driven by the action of the genotype constitutes the heritability of the character under study.

Random primer amplified polymorphic DNA (RAPD) In the classical polymerase chain reaction method, the primers used are known DNA sequences, whereas the RAPD technique relies on primers whose sequence is arbitrarily determined. RAPD primers are generally 10 bp long. The possible combinations are virtually unlimited. For a given genotype of a given individual or strain, different primers will reveal different polymorphisms. RAPDs are an extremely powerful method of exploring the genetic variability of organisms. However, their use in routine identification is limited by their lack of reproducibility.

Restriction fragment length polymorphism (RFLP) Variability in the DNA of a given organism evidenced by the use of bacterial restriction endonucleases. The endonuclease cuts the DNA at specific restriction sites characterized by given sequences, and the polymorphism of the DNA fragments thus obtained can be visualized on gels, either directly by ethidium bromide staining, or by Southern blot hybridization with specific probes.

Short tandem repeat polymorphism (STRP) Synonymous with microsatellites.

Single nucleotide polymorphism (SNP), Single-nucleotide Variant (SNV) Polymorphisms of one-letter variations in the DNA sequence. SNPs contribute to differences among individuals and populations. Most of them have no effect; others cause subtle differences in countless features, such as appearance, while some affect the risk for certain diseases. SNPs are widely used as high-resolution population markers and are the basic tool used in the so-called HapMap project. SNPs can be detected by: (1) restriction fragment length polymorphism, (2) sequencing, (3) denaturating high-performance liquid chromatography, (4) mass spectrometry, and (5) array-based resequencing/microarrays. SNPs constitute approximately 90% of all human genetic variations, and SNPs with a minor allele frequency of $\geq$1% occur every 100−300 bases throughout the human genome, on average. It is important to note that there are allelic frequency variations among different human populations, with the result that an SNP that is common in one geographical or ethnic group may be much rarer in another (see ancestry informative markers).

Sympatry Living in the same geographic location (see allopatry).

Transcription factor Protein that binds to specific genes, and modulates the rate of transcription of genetic information from DNA to messenger RNA.

REFERENCES

Alexander, D.H., Novembre, J., Lange, K., 2009. Fast model-based estimation of ancestry in unrelated individuals. Genome Research 19, 1655−1664.

Alves, I., Srámkovaá Hanulová, A., Foll, M., Excoffier, E., 2012. Genomic data reveal a complex making of humans. PLoS Genetics 8 (7), e1002837. http://dx.doi.org/10.1371/journal.pgen.1002837.

Arama, C., Maiga, B., Dolo, A., et al., 2015. Ethnic differences in susceptibility to malaria: what have we learned from immuno-epidemiological studies in West Africa? Acta Tropica 146, 152−156.

Armengol, L., Villatoro, S., González, J.R., et al., 2009. Identification of copy number variants defining genomic differences among major human groups. PLoS One e7230. http://dx.doi.org/10.1371/journal.pone.0007230.

Arvey, R.D., Bouchard Jr., T.J., Kaufman, N.L., et al., 1994. Mainstream science on intelligence. The Wall Street Journal. December 13.

Ashraf, Q., Galor, O., 2011. The "Out of Africa" Hypothesis, Human Genetic Diversity, and Comparative Economic Development. NBER Working Paper No. 17216, July 2011; JEL No. N10,N30,N50,O11,O50,Z10. http://www.nber.org/papers/w17216.

Auton, A., Bryc, K., Boyko, A.R., et al., 2009. Global distribution of genomic diversity underscores rich complex history of continental human populations. Genome Research 19, 795–803.

Avise, J.C., 2004. Molecular Markers, Natural History and Evolution, second ed. Chapman & Hall, New York, London.

Ayub, Q., Yngvadottir, B., Chen, Y., et al., 2013. FOXP2 targets show evidence of positive selection in European populations. The American Journal of Human Genetics 92, 696–706.

Barbujani, G., Colonna, V., 2010. Human genome diversity: frequently asked question. Trends in Genetics 26, 285–295.

Barbujani, G., Magagni, A., Minch, E., Cavalli-Sforza, L., 1997. An apportionment of human DNA diversity. Proceedings of the National Academy of Sciences of the United States of America 94, 4516–4519.

Belizário, J.E., 2013. The humankind genome: from genetic diversity to the origin of human diseases. Genome 56, 705–716.

Boas, F., 1912. Changes in the bodily form of descendants of immigrants. American Anthropologist 14, 530–562.

Bustamante, C.D., González Burchard, E., De La Vega, F.M., 2011. Genomics for the world. Nature 475, 163–165.

Cardona-Castro, N., Cortés, E., Beltrán, C., Romero, M., Badel-Mogollón, J.E., Bedoya, G., 2015. Human genetic ancestral composition correlates with the origin of *Mycobacterium leprae* strains in a leprosy endemic population. PLoS Neglected Tropical Diseases 9 (9), e0004045. http://dx.doi.org/10.1371/journal.pntd.0004045.

Casals, F., Bertranpetit, J., 2012. Human genetic variation, shared and private. Science 337, 39–40.

Cavalli-Sforza, L., 2007. Human evolution and its relevance for scientific epidemiology. Annual Review of Genomics and Human Genetics 8, 1–15.

Cavalli-Sforza, L.L., Feldman, M.W., 2003. The application of molecular genetic approaches to the study of human evolution. Nature Genetics (Suppl. 33), 266–275.

Cavalli-Sforza, L.L., Minch, E., Mountain, J.L., 1992. Coevolution of genes and languages revisited. Proceedings of the National Academy of Sciences of the United States of America 89, 5620–5624.

Chimpanzee Sequencing and Analysis Consortium, 2005. Initial sequence of the chimpanzee genome and comparison with the human genome. Nature 437, 69–87.

Cochran, G., Hardy, J., Harpending, H., 2006. Natural history of Ashkenazi intelligence. Journal of Biosocial Science 38, 659–693.

Cochran, G., Harpending, H., 2009. The 10,000 Year Explosion – How Civilization Accelerated Human Evolution. Basic Books. A member of the Perseus Books Group, New York.

Colonna, V., Ayub, Q., Chen, Y., et al., 2014. Human genomic regions with exceptionally high levels of population differentiation identified from 911 whole-genome sequences. Genome Biology 15, R88.

Conley, D., Fletcher, J., Dawes, C., 2014. The Emergence of Socio-Genomics. Contemporary Sociol 43, 458–467.

Conrad, D.F., Hurles, M.E., 2007. The population genetics of structural variation. Nature Genetics 39 (Suppl. 7), S30–S36.

Coon, C.S., 1962. The Origin of Races. Alfred A. Knopf, New York.

Currat, M., Excoffier, L., 2004. Modern humans did not admix with Neanderthals during their range expansion into Europe. PLoS Biology 2 (12), e421.

Demoule, J.P., 2014. Mais où sont passés les Indo-Européens? La librairie du XXIe siècle. Editions du Seuil, Paris.

Dobzhansky, T., 1966. L'Homme en évolution. Flammarion ed., Paris.

Daub, J.T., Hofer, T., Cutivet, E., Dupanloup, I., et al., 2013. Evidence for polygenic adaptation to pathogens in the human genome. Molecular Biology and Evolution 30, 1544–1558.

Edgar, H.J.H., 2009. Biohistorical approaches to ''Race'' in the United States: biological distances among African Americans, European Americans, and their ancestors. American Journal of Physical Anthropology 139, 58–67.

Edwards, A.W.F., 2003. Human genetic diversity: Lewontin's fallacy. BioEssays 25, 798–801.

Elhaik, E., Tatarinova, T., Chebotarev, D., et al., April 29, 2014. Nature Communications 5, 3513. http://dx.doi.org/10.1038/ncomms4513.

Enard, D., Messer, P.W., Petrov, D.A., 2015. Genome-wide signals of positive selection in human evolution. Genome Research 24, 885–895.

Evans, P.D., Gilbert, S.L., Mekel-Bobrov, N., et al., 2005. Microcephalin, a gene regulating brain size, continues to evolve adaptively in humans. Science 309, 1717–1720.

Evans, P.D., Mekel-Bobrov, N., Vallender, E.J., Hudson, R.R., Lahn, B.T., 2006. Evidence that the adaptive allele of the brain size gene microcephalin introgressed into *Homo sapiens* from an archaic *Homo* lineage. Proceedings of the National Academy of Sciences of the United States of America 103, 18178–18183.

Fraser, H.B., 2013. Gene expression drives local adaptation in humans. Genome Research 23, 1089–1096.

Fu, W., Akey, J.M., 2013. Selection and adaptation in the human genome. Annual Review of Genomics and Human Genetics 14, 467–489.

Fu, W., O'Connor, T.D., Jun, G., et al., 2013. Analysis of 6,515 exomes reveals the recent origin of most human protein-coding variants. Nature 493, 216–220.

Fumagalli, M., Moltke, I., Grarup, N., et al., 2015. Greenlandic Inuit show genetic signatures of diet and climate adaptation. Science 349, 1343–1346.

Galanter, J.M., Fernandez-Lopez, J.C., Gignoux, C.R., et al., 2012. Development of a panel of genome-wide ancestry informative markers to study admixture throughout the Americas. PLoS Genetics 8 (3), e1002554. http://dx.doi.org/10.1371/journal.pgen.1002554.

Gallego Llorente, M., Jones, E.R., Eriksson, A., et al., 2015. Ancient Ethiopian genome reveals extensive Eurasian admixture throughout the African continent. Science (online). http://www.sciencemag.org/content/early/2015/10/07/science.aad2879.

Gibbons, A., 2015. Humanity's long, lonely road. Science 349, 1270.

Gonzaga-Jauregui, C., Lupski, J.R., Gibbs, R.A., 2012. Human genome sequencing in health and disease. Annual Review of Medicine 63, 35–61.

González Burchard, E., Ziv, E., Coyle, N., et al., 2003. The importance of race and ethnic background in biomedical research and clinical practice. The New England Journal of Medicine 348, 1170–1175.

Gould, S.J., 1981. The Mismeasure of Man. W. W. Norton and Company, New York.

Gould, S., 2000. "The spice of life". Leader to Leader 15, 19–28.

Gould, S.J., Lewontin, R.C., 1979. The spandrels of San Marco and the Panglossian paradigm: a critique of the adaptationist programme. Proceedings of the Royal Society of London B 205, 581–598.

Grossman, S.R., Andersen, K.G., Shlyakhter, I., et al., 2013. Identifying recent adaptations in large-scale genomic data. Cell 152, 703–713.

Guha, S., Rosenfeld, J.A., Malhotra, A.K., et al., 2012. Implications for health and disease in the genetic signature of the Ashkenazi Jewish population. Genome Biology 13, R2.

Günther, T., Valdiosera, C., Malmström, H., et al., 2015. Ancient genomes link early farmers from Atapuerca in Spain to modern-day Basques. Proceedings of the National Academy of Sciences of the United States of America 112, 11917–11922.

Gurdasani, D., Carstensen, T., Tekola-Ayele, F., et al., 2015. The African Genome Variation Project shapes medical genetics in Africa. Nature 517, 327–332.

Haak, W., Lazaridis, L., Patterson, N., et al., 2015. Massive migration from the steppe was a source for Indo-European languages in Europe. Nature 522, 207–211.

Harpending, H., 2002. Race. Population genetics perspective. In: Pagel, M. (Ed.), Encyclopedia of Evolution, pp. 979–981.

Hawks, J., Wang, E.T., Cochran, G.M., Harpending, H.C., Moyzis, R.K., 2007. Recent acceleration of human adaptive evolution. Proceedings of the National Academy of Sciences of the United States of America 104, 20753–20758.

Hellenthal, G., Busby, G.B.J., Band, G., et al., 2014. A genetic atlas of human admixture history. Science 343, 747–751.

Henn, B.M., Botigué, L.R., Bustamante, C.D., Clark, A.G., Gravel, S., 2015. Nature Reviews Genetics 16, 333–343.

Hennig, W., 1966. Phylogenetic Systematics. University of Illinois Press, Urbana, Illinois.

Heyn, H., Moran, S., Hernando-Herraez, I., et al., 2013. DNA methylation contributes to natural human variation. Genome Research 23, 1363–1372.

Hooton, E.A., 1926. Methods of racial analysis. Science 63, 75–81.

Hunley, K.L., Healy, M.E., Long, J.C., 2009. The global pattern of gene identity variation reveals a history of long-range migrations, bottlenecks, and local mate exchange: implications for biological race. American Journal of Physical Anthropology 139, 35–46.

Jablonski, N.G., Chaplin, G., 2012. Human skin pigmentation, migration and disease susceptibility. Philosophical Transactions of the Royal Society B 367, 785–792.

Jakobsson, M., Scholz, S.W., Scheet, P., et al., 2008. Genotype, haplotype and copy-number variation in worldwide human populations. Nature 451, 998–1003.

Jordan, B., 2008. L'humanité au pluriel. La génétique et la question des races. Editions du Seuil, Paris.

Jorde, L.B., Wooding, S.P., 2004. Genetic variation, classification and "race". Nature Genetics 36 (Suppl. 11), S28–S32.

Karlsson, E.K., Kwiatkowski, D.P., Sabeti, P.C., 2014. Natural selection and infectious disease in human populations. Nature Reviews Genetics 15, 379–383.

Keita, S.O.Y., Kittles, R.A., Royal, C.D.M., et al., 2004. Conceptualizing human variation. Nature Genetics 36 (Suppl. 11), S17–S20.

King, M.C., Wilson, A.C., 1975. Evolution at two levels in humans and chimpanzees. Science 188, 107–116.

Krause, J., Lalueza-Fox, C., Orlando, L., et al., 2007. The derived FOXP2 variant of modern humans was shared with Neandertals. Current Biology 17, 1908–1912.

Lachance, J., Tishkoff, S.A., 2013. Population genomics of human adaptation. Annual Review of Ecology, Evolution, and Systematics 44, 123–143.

Lahn, B.T., Ebenstein, L., 2009. Let's celebrate human genetic diversity. Nature 461, 726–728.

Laland, K.N., Odling-Smee, J., Myles, S., 2010. How culture shaped the human genome: bringing genetics and the human sciences together. Nature Reviews Genetics 11, 137–148.

Lander, E.S., 2011. Initial impact of the sequencing of the human genome. Nature 470, 187–197.

Lawler, J.M., 1978. IQ, Heritability, and Racism. International Publishers, New York.

Lazaridis, I., Patterson, N., Mittnik, A., et al., 2014. Ancient human genomes suggest three ancestral populations for present-day Europeans. Nature 513, 409–413.

Leroi, A.M., March 14, 2005. A Family Tree in Every Gene. The New York Times.

Leslie, S., Winney, B., Hellenthal, G., et al., 2015. The fine-scale genetic structure of the British population. Nature 519, 309–314.

Levy-Strauss, C., 1952. Race et histoire. Editions Denoël, Paris.

Lewis, J.E., DeGusta, D., Meyer, M.R., et al., 2011. The mismeasure of science: Stephen Jay Gould versus Samuel George Morton on skulls and bias. PLoS Biology 9 (6), e1001071. http://dx.doi.org/10.1371/journal.pbio.1001071.

Lewontin, R.C., 1972. The apportionment of human diversity. Evolutionary Biology 6, 381–398.

Lewontin, R.C., Hartl, D.L., 1991. Population genetics in forensic DNA typing. Science 254, 1745–1750.

Li, J.Z., Absher, D.M., Tang, H., et al., 2008. Worldwide human relationships inferred from genome-wide patterns of variation. Science 319, 1100–1104.

Long, J.C., Li, J., Healy, M.E., 2009. Human DNA sequences: more variation and less race. American Journal of Physical Anthropology 139, 23–34.

Longobardi, G., Ghirotto, S., Guardiano, C., et al., 2015. Across language families: genome diversity mirrors linguistic variation within Europe. American Journal of Physical Anthropology 157, 630–640.

López Herráez, D., Bauchet, M., Tang, K., et al., 2009. Genetic variation and recent positive selection in worldwide human populations: evidence from nearly 1 million SNPs. PLoS One 4 (11), e7888. http://dx.doi.org/10.1371/journal.pone.0007888.

Manica, A., Amos, W., Balloux, F., Hnihara, T., 2007. The effect of ancient population bottlenecks on human phenotypic variation. Nature 448, 346–349.

Manry, J., Quintana-Murci, L., 2013. A genome-wide perspective of human diversity and its implications in infectious disease. Cold Spring Harbor Perspectives in Medicine 3, a012450.

Martin, A.R., Costa, H.A., Lappalainen, T., et al., 2014. Transcriptome sequencing from diverse human populations reveals differentiated regulatory architecture. PLoS Genetics 10 (8), e1004549. http://dx.doi.org/10.1371/journal.pgen.1004549.

Mathieson, I., Lazaridis, I., Rohland, N., et al., 2015. Eight Thousand Years of Natural Selection in Europe. Preprint at bioRxiv at. http://doi.org/4wt.

Mathieson, I., McVean, G., 2012. Differential confounding of rare and common variants in spatially structured populations. Nature Genetics 44, 243–246.

Mayr, E., 1963. Animal Species and Evolution. Belknap Press of Harvard University Press, Cambridge.

Mekel-Bobrov, N., Gilbert, S.L., Evans, P.D., et al., 2005. Ongoing adaptive evolution of ASPM, a brain size determinant in *Homo sapiens*. Science 309, 1720–1722.

Mersha, T.B., Abebe, T., 2015. Self-reported race/ethnicity in the age of genomic research: its potential impact on understanding health disparities. Human Genomics. http://dx.doi.org/10.1186/s40246-014-0023-x.

Mitton, J.B., 1977. Genetic differentiation of races of man as judged by single-locus and multilocus analyses. The American Naturalist 111, 203–212.

Mitton, J.B., 1978. Measurement of differentiation: reply to Lewontin, Powell, and Taylor. The American Naturalist 112, 1142–1144.

Moreno-Estrada, A., Gignoux, C.R., Fernández-López, J.C., et al., 2014. The genetics of Mexico recapitulates Native American substructure and affects biomedical traits. Science 344, 1280–1285.

Morning, A., 2014. Does genomics challenge the social construction of race? Sociological Theory 32, 189–207.

Morton, S.G., 1849. Catalogue of Skulls of Man and the Inferior Animals, third ed. Merrihew and Thomson Printers, Philadelphia.

Morwood, M.J., van Oosterzee, P., 2007. The Discovery of the Hobbit: The Scientific Breakthrough that Changed the Face of Human History. Random House, Sydney.

Mountain, J.L., Risch, N., 2004. Assessing genetic contribution to phenotypic differences among "racial" and "ethnic" groups. Nature Genetics 36 (Suppl. 11), S48–S53.

Need, A.C., Kasperavičiūtė, D., Cirulli, E.T., Goldstein, D.B., 2009. A genome-wide genetic signature of Jewish ancestry perfectly separates individuals with and without full Jewish ancestry in a large random sample of European Americans. Genome Biology 10, R7.

Nei, M., 1978. The theory of genetic distance and evolution of human races. Japanese Journal of Human Genetics 23, 341–369.

Nei, M., Roychoudhury, A.K., 1993. Evolutionary relationships in human populations on a global scale. Molecular Biology and Evolution 10, 927–943.

Nelson, M.R., Wegmann, D., Ehm, M.G., et al., 2012. An abundance of rare functional variants in 202 drug target genes sequenced in 14,002 people. Science 337, 100–104.

Novembre, J., Han, E., 2012. Human population structure and the adaptive response to pathogen-induced selection pressures. Philosophical Transactions of the Royal Society B 367, 878–886.

Novembre, J., Johnson, T., Bryc, K., et al., 2008. Genes mirror geography within Europe. Nature 456, 98–101.

Novembre, J., Ramachandran, S., 2011. Perspectives on human population structure at the cusp of the sequencing era. Annual Review of Genomics and Human Genetics 12, 245–274.

Ostrer, H., Skorecki, K., 2013. The population genetics of the Jewish people. Human Genetics 132, 119–127.

Ousley, S., Jantz, R., Freid, D., 2009. Understanding race and human variation: why forensic anthropologists are good at identifying race. American Journal of Physical Anthropology 139, 68–76.

Parra, E.J., Kittles, R.A., Shriver, M.D., 2004. Implications of correlation between skin color and genetic ancestry for biomedical research. Nature Genetics 36 (Suppl. 11), S54–S60.

Pfaff, C.L., Parra, E.J., Bonilla, C., et al., 2001. Population structure in admixed populations: effect of admixture dynamics on the pattern of linkage disequilibrium. The American Journal of Human Genetics 6, 198–207.

Pickrell, J.K., Coop, G., Novembre, J., et al., 2009. Signals of recent positive selection in a worldwide sample of human populations. Genome Research 19, 826–837.

Pickrell, J.K., Reich, D., 2014. Toward a new history and geography of human genes informed by ancient DNA. Trends in Genetics 30, 377–389.

Pigliucci, M., 2013. What are we to make of the concept of race? Thoughts of a philosopher–scientist. Studies in History and Philosophy of Biological and Biomedical Science 44, 272–277.

Pritchard, J.K., Pickrell, J.K., Coop, G., 2009. The genetics of human adaptation: hard sweeps, soft sweeps, and polygenic adaptation. Current Biology 20, R208–R213.

Pritchard, J.K., Stephens, M., Donnelly, P., 2000. Inference of population structure using multilocus genotype data. Genetics 155, 945–959.

Prugnolle, F., Manica, A., Balloux, F., 2005. Geography predicts neutral genetic diversity of human populations. Current Biology 15, R159–R160.

Racimo, F., Sankararaman, S., Nielsen, R., Huerta-Sánchez, E., 2015. Evidence for archaic adaptive introgression in humans. Nature Reviews Genetics 16, 359–371.

Relethford, J.H., 2009. Race and global patterns of phenotypic variation. American Journal of Physical Anthropology 139, 16–22.

Richardson, S.S., 2011. Race and IQ in the postgenomic age: the microcephaly case. BioSocieties 6, 420–446.

Richerson, P.J., Boyd, R., Henrich, J., 2010. Gene-culture coevolution in the age of genomics. Proceedings of the National Academy of Sciences of the United States of America 107 (Suppl. 2), 8985–8992.

Risch, N., Burchard, E., Ziv, E., Tang, H., 2002. Categorization of humans in biomedical research: genes, race and disease. Genome Biology 3 (7) comment2007.1–comment2007.12.

Risch, N., Choudhry, S., Via, M., et al., 2009. Ancestryrelated assortative mating in Latino populations. Genome Biol 10, R132.

Romualdi, C., Balding, D., Naside, I.S., et al., 2002. Patterns of human diversity, within and among continents, inferred from biallelic DNA polymorphisms. Genome Research 12, 602–612.

Rosenberg, N.A., Pritchard, J.K., Weber, J.L., et al., 2002. Genetic structure of human populations. Science 298, 2381–2385.

Rosenberg, N.A., Mahajan, S., Ramachandran, S., et al., 2005. Clines, clusters, and the effect of study design on the inference of human population structure. PLoS Genetics 1 (6), e70.

Rowell, J.L., Dowling, N.F., Yu, W., et al., 2012. Trends in population-based studies of human genetics in infectious diseases. PLoS One 7 (2), e25431. http://dx.doi.org/10.1371/journal.pone.0025431.

Ruff, C.B., Holt, B., Niskanen, M., et al., 2015. Gradual decline in mobility with the adoption of food production in Europe. Proceedings of the National Academy of Sciences of the United States of America 112, 7147–7152.

Rushton, J.P., Jensen, A.R., 2006. The totality of available evidence shows the race IQ gap still remains. Psychological Science 17, 921–922.

Sarich, V., Miele, F., 2004. Race: The Reality of Human Differences. Westview Press, Boulder, Colorado, USA.

Serre, D., Pääbo, S., 2004. Evidence for gradients of human genetic diversity within and among continents. Genome Research 14, 1679–1685.

Shiao, J.L., 2014. Response to HoSang; Fujimura, Bolnick, Rajagopalan, Kaufman, Lewontin, Duster, Ossorio, and Marks; and Morning. Sociological Theory 32, 244–258.

Shiao, J.L., Bode, T., Beyer, A., Selvig, D., 2012. The genomic challenge to the social construction of race. Sociological Theory 30, 67–88.

Shriver, M.D., Kennedy, G.C., Parra, E.J., et al., 2004. The genomic distribution of population substructure in four populations using 8,525 autosomal SNPs. Human Genomics 1, 274–286.

Sparks, C.S., Jantz, R.L., 2002. A reassessment of human cranial plasticity: Boas revisited. Proceedings of the National Academy of Sciences of the United States of America 99, 14636–14639.

Spielman, R.S., Bastone, L.A., Burdick, J.T., et al., 2007. Common genetic variants account for differences in gene expression among ethnic groups. Nature Genetics 39, 226–231.

Stearns, S.C., Byars, S.G., Diddahally, R., Govindaraju, D.R., Ewbank, D., 2010. Measuring selection in contemporary human populations. Nature Reviews Genetics 11, 611–622.

Stoneking, M., Krause, J., 2011. Learning about human population history from ancient and modern genomes. Nature Reviews Genetics 12, 603–614.

Stranger, B.E., Nica, A.C., Forrest, M.S., et al., 2007. Population genomics of human gene expression. Nature Genetics 39, 1217–1224.

Stringer, C.B., Andrews, P., 1988. The origin of modern humans. Science 239, 1263–1268.

Sudmant, P., Kitzmann, J.O., Antonacci, F., et al., 2010. Diversity of human copy number variation and multicopy genes. Science 330, 641–646.

Sudmant, P.H., Mallick, S., Nelson, B.J., et al., 2015a. Global diversity, population stratification, and selection of human copy-number variation. Science. http://dx.doi.org/10.1126/science.aab3761.

Sudmant, P.H., Rausch, T., Gardner, E.J., et al., 2015b. An integrated map of structural variation in 2,504 human genomes. Nature 526, 75–81.

Tang, H., Quertermous, T., Rodriguez, B., et al., 2005. Genetic structure, self-identified race/ethnicity, and confounding in case-control association studies. The American Journal of Human Genetics 76, 268–275.

Templeton, A.R., 2012. Gene flow, haplotype patterns and modern human origins. In: eLS. John Wiley & Sons, Ltd, Chichester. http://dx.doi.org/10.1002/9780470015902.a0020795.pub2.

Templeton, A.R., 2013. Biological races in humans. Studies in History and Philosophy of Biological and Biomedical Science 44, 262–271.

Tennessen, J.A., Akey, J.M., 2011. Parallel adaptive divergence among geographically diverse human populations. PLoS Genetics 7 (6), e1002127. http://dx.doi.org/10.1371/journal.pgen.1002127.

Tennessen, J.A., Bigham, A.W., O'Connor, T.D., et al., 2012. Evolution and functional impact of rare coding variation from deep sequencing of human exomes. Science 337, 64–69.

The 1000 Genomes Project Consortium, 2012. An integrated map of genetic ariation from 1,092 human genomes. Nature 491, 56–65.

The 1000 Genomes Project Consortium, 2015. A global reference for human genetic variation. Nature 526, 68–74.

The UK10K Consortium, 2015. The UK10K project identifies rare variants in health and disease. Nature 526, 82–89.

Tibayrenc, M., 2004. The impact of human genetic diversity in the transmission and severity of infectious diseases. In: Dronamraju, K. (Ed.), Infectious Disease: Host-Pathogen Evolution. Cambridge University Press, pp. 315–324.

Tibayrenc, M., 2007a. Human genetic diversity and epidemiology of parasitic and other transmissible diseases. Advances in Parasitology 64, 378–428.

Tibayrenc, M., 2007b. Human genetic diversity and the spread of infectious diseases. In: Tibayrenc, M. (Ed.), Encyclopedia of Infectious Diseases: Modern Methodologies. Wiley & Sons, pp. 321–335.

Tibayrenc, M., Ayala, F.J., 2012. Reproductive clonality of pathogens: a perspective on pathogenic viruses, bacteria, fungi, and parasitic protozoa. Proceedings of the National Academy of Sciences of the United States of America 109 (48), E3305–E3313.

Tibayrenc, M., Ayala, F.J., 2013. How clonal are *Trypanosoma* and *Leishmania*? Trends in Parasitology 29, 264–269.

Tishkoff, S., 2015. Strength in small numbers. Science 349, 1282–1283.

Tishkoff, S.A., Kidd, K.K., 2004. Implications of biogeography of human populations for "race" and medicine. Nature Genetics 36 (Suppl. 11), S21–S27.

Vallois, H.V., 1976. Les Races Humaines. Presses Universitaires de France, Paris.

Vasseur, E., Quintana-Murci, L., 2013. The impact of natural selection on health and disease: uses of the population genetics approach in humans. Evolutionary Applications 6, 596–607.

Vernot, B., Stergachis, A.B., Maurano, M.T., et al., 2012. Personal and population genomics of human regulatory variation. Genome Research 22, 1689–1697.

Voight, B.F., Kudaravalli, S., Wen, X., Pritchard, J.K., 2006. A map of recent positive selection in the human genome. PLoS Biology 4 (3), e72.

Wade, N., 2014. A Troublesome Inheritance. Genes, Race and Human History. Penguin Books, New York.

Wang, C., Zöllner, S., Rosenberg, N.A., 2012. A quantitative comparison of the similarity between genes and geography in worldwide human populations. PLoS Genetics 8 (8), e1002886. http://dx.doi.org/10.1371/journal.pgen.1002886.

Weidenreich, F., 1946. Apes, Giants, and Man. University of Chicago Press, Chicago, IL.

Wilde, S., Timpson, A., Kirsanow, K., et al., 2014. Direct evidence for positive selection of skin, hair, and eye pigmentation in Europeans during the last 5,000 y. Proceedings of the National Academy of Sciences of the United States of America 111, 4832–4837.

Wolpoff, M.H., 2009. How Neandertals inform human variation. American Journal of Physical Anthropology 139, 91–102.

Woodley, M.A., Rindermann, H., Bell, E., Stratford, J., Piffer, D., 2014. The relationship between Microcephalin, ASPM and intelligence: a reconsideration. Intelligence 44, 51–63.

Wright, S., 1978. Evolution and the Genetics of Populations, Vol. 4, Variability Within and Among Natural Populations. University of Chicago Press, Chicago, IL.

Zietsch, B.P., de Candia, T.R., Keller, M.C., 2015. Evolutionary behavioral genetics. Current Opinion in Behavioral Sciences 2, 73–80.

Chapter 7

Evolution and Implications of Genomic Diversity on "Human Kind" in India

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INTRODUCTION

India is the greatest story of humankind told until now, as a six-part BBC historical documentary series reveals (Wood, 2007; "The story of India," Youtube.com). As an ancient civilization, India has become the world's largest democracy; one can reflect on and admire the determining factors in India's success. The Indian subcontinent and its people are more diverse than anywhere else in the world in terms of its gene pool, culture, and landscape (Shastri, 1976). This was the result of the first coastal Southern route migration ~60,000 ybp, and the subsequent migrations, which led to many autochthonous evolution of its lineages (Mellars et al., 2013; Underhill et al., 2001; Wells et al., 2001). The early settlers were isolated in various niches of India, particularly in hilly tracts, while later migrants occupied the plains and river beds (Sahoo et al., 2006; Sanghvi et al., 1981). The later migrants formed self-sustainable demes in various niches, resulting in enormous diversity and absorption of the first coastal migrants into their fold (ArunKumar et al., 2012b). The degree of natural selection that operated on these demes through infectious diseases and bottlenecks, in addition to population level forces like migration and miscegenation, is still an enigma (Norman et al., 2007; Rajalingam et al., 2008). Nevertheless, we can obtain evidence for many of these factors that operated on the Indian gene pool to make it a diverse region (Pitchappan, 1988, 2002; Shanmugalakshmi et al., 2003).

The Indian population has been broadly classified into tribes and castes. The primitiveness of their traits, distinctive culture, geographical isolation, shyness of contact, and backwardness are all characterized as scheduled tribes (STs) deserving constitutional preferences (Ministry of Tribal Affairs, 2015). The STs forming 8.6% of Indian populations in 2011 are concentrated in Central India (20%–40% of total population) and the Northeast, particularly Arunachal Pradesh and areas surrounding Assam (>40%) (Ministry of Tribal Affairs, 2015), while castes live mostly in plains and river-bed civilizations, with the highest proportion of castes in Indo-Gangetic doab and Tamil Nadu/Kerala, the Southern part of the Deccan Plateau, with <5% STs. It is interesting to note that after independence, Indian states (from now, referred to as States) were reorganized as linguistic states based on the premise that people speaking a given language share similar cultures within a restricted geographical region (Ambedkar, 1956). Though this may be true at times, it has never been true all of the time. The genetic polymorphisms of Indian populations have thrown light on their diversity and affinity to the world populations (Arunkumar et al., 2012a; Balakrishnan et al., 1996; Pitchappan, 2002; Pitchappan et al., 1984, 1997). These studies have revealed the regional differences and social structure that correlated to many genetic, physical, and cultural-anthropological characteristics (ArunKumar et al., 2012b, 2015a,b; Sanghvi et al., 1981; Shanmugalakshmi et al., 2003; Underhill et al., 2010). Contrary to the common notion, tribes were not always drawn from the early settlers of the region as some of them were drawn from later migrations. A classical example in the state of Tamil Nadu are the ancient tribes Paliyar, Pulayar, Paniyar, Kadar, and Irula with ancient NRY clade F* while the Toda and Kota are the later migrants with their animal husbandry and metallurgy; the later cluster with Brahmin-related populations in their NRY Rs and Js of the Neolithic people and Central Asian populations (ArunKumar et al., 2012b). The gene pool of each state is thus never panmictic,

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00007-7

and the "intrastate" diversity of various demes is greater than the interstate diversity (Majumder, 1998). Understanding the causes of this diversity will help in understanding better the role of the immunogenome in health and diseases.

A major genome block involved in immune and inflammatory responses are strewn in the major histocompatibility complex (MHC) region located in the short arm of chromosome 6 (Trowsdale and Knight, 2013). The investigations on MHC and non-MHC gene profiles in various populations of peninsular India and the Deccan, and their correlates to health and disease, have revealed enormous diversity, a result of sympatric isolation (Jayalakshmi et al., 2012; Pitchappan, 2002). Various demes and population groups show diverse genetic profiles, suggesting a differential susceptibility to infectious diseases such as leprosy, tuberculosis (TB), and HIV (Brahmajothi et al., 1991; Jagannathan et al., 2011; Ravikumar et al., 1999; Siddiqui et al., 2001). Many of these diseases do have unique epidemiological profiles in their distribution and manifestations; not all these demes and population groups may be equally susceptible to a given epidemic (Pitchappan, 2002). There are three partners in determining the outcome of an infectious disease, viz., pathogen, host, and environment. As we know, most diseases have a nature—nurture relationship, and we need to study all three partners and their diversity on the same cohort to understand a disease. The existence of varied gene pools—populations and demes—in different States make each State unique and adds a new dimension to the disease studies.

With the advent of DNA technology, biology has become a more exact science and it is now possible to draft a well-designed study inclusive of all the confounding factors mentioned above. This essentially needs to cover the local epidemiological scenario, genetic landscape of the population, country investigated, and the nature of the disease. Here we review our understanding of the peopling of India, how the early settlers contributed to the diversity of the gene pool of India, and how later migration and cultural evolution shaped this diversity and the resultant immunogenome diversity, and we argue how one can make use of these variables to study disease processes.

PEOPLING OF INDIA

Early Settlers

Homo sapiens sapiens arrived in India some 60,000 ybp (Wells et al., 2001), which was the Southern route and the coastal highway to reach Australia (Cavalli-Sforza et al., 1994). The sea was low at that time, making Indonesia one land mass, which allowed them to walk through the coastal belt (https://www.youtube.com/watch?v=-dDXIX-y6aY). As a result of this early migration, some people stayed enroute giving rise to some isolated groups, the signature of which we see even today in both the tribal and caste populations of India (Arunkumar et al., 2012a,b; Zhong et al., 2010). We hasten to add that the tribe and caste designations were originally described by the anthropologists of the past, and the classifications could change. As per the constitution of India these tribes have been provided with special incentives and privileges to uplift their standard of living. All these tribes have not been derived from the earlier settlers alone. Most of them live in difficult niches in hilly tracts and dense forest covers, isolated from the rest of the plains populations; but early Neolithic people who settled in these regions also took up isolated lifestyle to be called as tribes, as in the case of Toda and Kota tribes of Tamil Nadu (ArunKumar et al., 2012b).

In 2001 we identified the descendants of the first coastal migration to India, carrying the marker NRY HG C-M130 in Tamil Nadu (Arunkumar et al., 2012a; Wells et al., 2001). This first coastal migration left the sporadic NRY HG C-M130 marker, the marker for out-of-Africa (OOA) migration, estimated ~60,000 years old, mostly in the Western Ghats, Eastern plains, and sporadically across Northeast and Central India. The NRY HG F*-M89 representing the second wave, with an estimated age of ~55,000 years, has been very successful, and as of today, 90% of the world population is the descendant of these ancestors. A serial founder effect with successive bottlenecks during range expansion progressively reduced the genetic and phenotypic diversity with distance from Africa, and a similar founder effect seems to have operated on human culture and languages as well (Atkinson, 2011; Ramachandran et al., 2005). In India the NRY clade F*-M89 is seen in many populations of the Deccan and Southern India and sporadically in Gujarat and Northeast, interestingly without any distinction of castes and tribes (ArunKumar et al., 2012b). Many lineages of this clade have expanded and have been very successful in India, characterizing various demes.

Autochthonous Expansions

Under the aegis of the Genographic, a global collaborative study (www.genographic.com), we have now studied ~11,527 male samples from 91 tribes and 129 castes, for their NRY and mtDNA polymorphisms. The study has revealed a nonuniform pattern of distribution of NRY and mtDNA clades in different states and regions of India (Watkins et al., 2008). NRY HG H-M69 and its clades are unique and ubiquitous in most parts of India except Arunachal Pradesh and Nepal (The Genographic—Madurai, unpublished, Fig. 7.1; Underhill et al., 2001). On the other hand, NRY HG L1-M27, considered as a marker for Dravidian (Sengupta et al., 2006), is present in most parts of India with the highest frequency and diversity

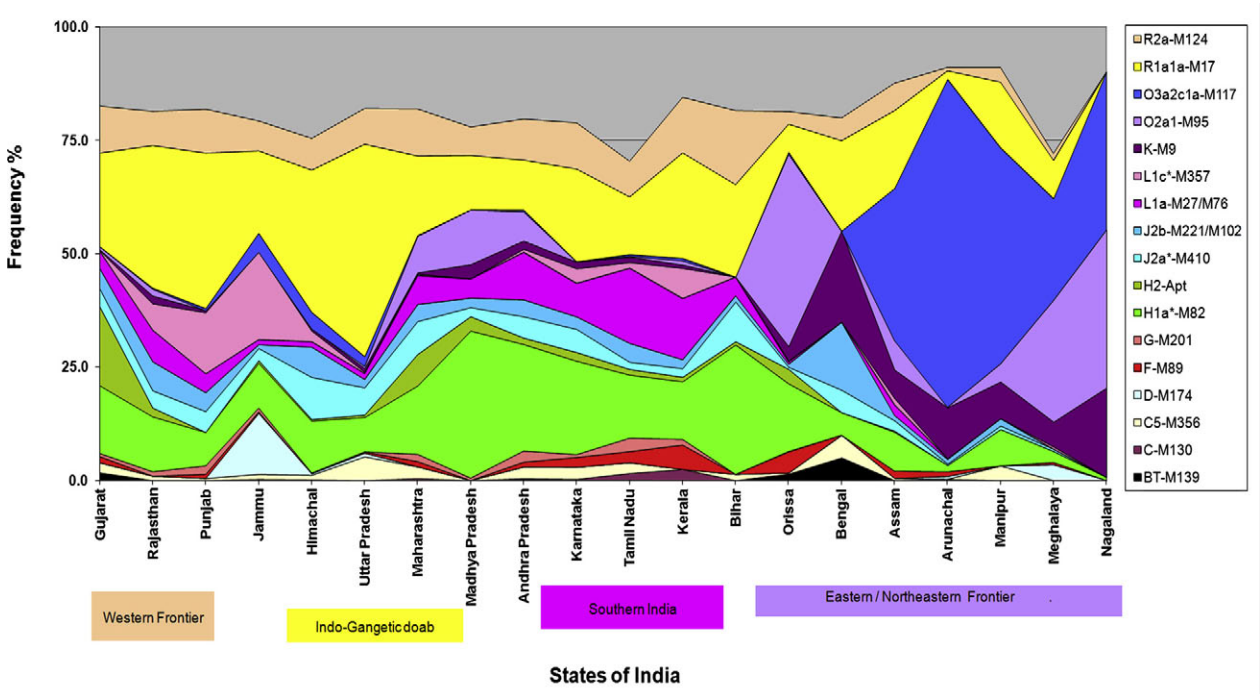

FIGURE 7.1 Distribution of major Non recombinant Y Haplo group (NRY HG) in various states of India. Major alleles are distributed in most of the states though in varied proportions. Thus the Indo-Gangetic doab and Western Frontier are characterized by R1a1, East by O2a, O3a3, and K, and Southern India by L1a. Nonetheless at the exact population/deme level (caste/tribe) there is enormous variation as shown in our Tamil Nadu paper (ArunKumar et al., 2012b). A similar trend prevails in various States of India. *Compiled based on "The Genographic India" data set of 11,420 samples.*

in Tamil Nadu, Karnataka, and Andhra (Fig. 7.1), and it is absent in Assam, Bengal, Northeast, and Himalayas. On the contrary, the marker for Austroasiatic speakers NRY HG O2a-M95 is restricted to the East and parts of Central and Northeast India (Arunkumar et al., 2015b; Kumar et al., 2007). The NRY R clades, R1a1-M17 and R2-M124, are present in highest frequencies in Indo-Gangetic doab region, particularly Uttar Pradesh, Bihar, and Western India (Fig. 7.1). The literature and our study have thus shown evolution and autochthonous expansion of many new NRY clades in India: a small founder settling in a niche, bottleneck, and a huge uninterrupted expansion might have lead to the current scenario. Since it has now been confirmed that the genetics correlate with the linguistics, particularly various NRY clades, it suggests that this was the trend from the very beginning of OOA exodus, and it makes one wonder whether language was instrumental to various cultural evolutions with better communication tools (Arunkumar et al., 2012a, 2015b; Atkinson, 2011; Balanovsky et al., 2011; Quintana-Murci and Fellous, 2001; Semino et al., 2004).

Arrival of Neolithic Farmers

The origin and expansion of various populations in different niches of India have been well documented. These early settlers further received many gene pools and migrations from both East and the West of India during the Neolithic period (Kivisild et al., 1999; Renfrew, 1996). Males with NRY HG O2a-M95 arrived at the Northeastern frontiers 10,000−5000 ybp, from Laos with their Austroasiatic tongue to expand and give rise to the Munda language (Arunkumar et al., 2015b; Chaubey et al., 2011). Similarly from the West, many streams of Neolithic people came in from Central Asia with their technology and cattle rearing. These include people with NRY HGs J-M304 and R-M207 male chromosomes (Basu et al., 2003; McElreavey and Quintana-Murci, 2005). The most successful expansion within the NRY HG R-M207 clade was R1a1-M17 and R2-M124 people with Indo-European tongue spreading into the whole of Indo-Gangetic doab, and North of Vindhyas. Paradoxically the rice cultivation thought to be a technology of the eastern world was well adopted by these people, and wetland agriculture was successfully implemented in both Northern and Southern India (Bellwood et al., 2002; Fuller, 2006; Higham, 2002; Trivedi et al., 2008). Rice was not common in the early Harappan phase (Kochhar, 2000) and it was brought from the northeast to India (Higham, 2002). While the demic expansion may explain the various language speakers and their cultures, the rice cultivar adoption implies a quick technology change.

Population Stratification

At the dawn of independence, scholars of India debated and carved out various administrative provinces as linguistic states, since the people speaking a given language shared similar cultures (Ambedkar, 1956). Many studies have also proved that these might be true at the gene pool level as well, for various languages are restricted to different geographical regions of India—the Indo-European speakers in the North; Austroasiatic and Tibeto-Burmese speakers to the East and Northeast, respectively; and Dravidian in the Deccan/South (ArunKumar et al., 2012b, 2015b; Sanghvi et al., 1981; Thapar, 1995). In most of the states the intrastate diversity is greater than the interstate diversity, though very definite Y chromosome signatures reflect on the whole genome, irrespective of their present-day distribution in India (ArunKumar et al., 2015a; Majumder, 2008). As mentioned earlier, the enormous degree of regional differences in gene pool and population stratification of various kinds is attributed to their history of migration, settlement, and expansion, and serial founder effect (Ramachandran et al., 2005). Nonetheless, it was observed that the mode of subsistence is the most powerful tool of this isolation and stratification in the early migrants (ArunKumar et al., 2012b).

Enigma of Dravidian Land

Among various states of India, Tamil Nadu is the Southernmost region of the Deccan and the heartland of Dravidian cultural evolution. Dravidian also includes a group of people who share cultural practices and values. Their characteristic cross-cousin marriages and place names are shared with Gujarat and Maharashtra states as well (Fuller, 2007; Southworth, 2005a,b; Trautmann, 1981), proposing a relationship between the people of these two regions, though the continuum of this culture and place names are absent in the intervening regions. The Dravidian language Tamil has a very ancient literary tradition dating back to second millennium BC and many ancient literary works describe a well stratified, occupationally specialized society; the earliest literary work itself, a grammar by Tholkappiar, a Brahman, implies that the spoken language must have been in vogue at least a few millennia earlier to that period. The great epics of Sangam literature, such as Agananuru and Purnananuru, depict early life style of eloping and marriages, and a hunter-gatherer mode of subsistence. The Sangam literature Silappathikaram depicts the lifestyle of a well-organized society and various religious thoughts 2000 ybp. Our study has revealed that the identified population stratification of Tamil Nadu crystallized 7000 ybp and no admixture between the identified subsistence-based demes took place during the past 3000 years (ArunKumar et al., 2012b). Thus the mode of subsistence, such as fishery in the coast, dry land farming in the interior rain shadow regions, and foraging, hunting, and gathering in the hilly tracts played a dominant role in determining the lifestyle and technology of these demes, giving rise to the stratified society of Tamil Nadu. This is indeed much earlier to the formation of castes that was ushered in with the arrival of wet land irrigation, settled agriculture, private land holdings, and crystallization of religious ethos (Champaklakshmi, 2001). Both geographical and cultural isolation sufficiently lead them to inbreed amongst themselves resulting in unique genetic signatures in each one of them. Thus the present day hill tribes of Western Ghats are characterized by NRY HG F*-M89, an ancient marker (~55,000 ybp), the dry land farmers (DLF) of the Western Ghat rain shadow regions and plains accounting for about 50% of Tamil Nadu (TN) population by NRY HG L1-M20, a characteristic of Dravidian (Sengupta et al., 2006) and Vellala and Brahmin—related populations by NRY HG R1a1-M17 and R2-M205 (Bamshad et al., 2001; Sharma et al., 2009).

Deccan, Dry Land Farmers, and NRY HG L1

If we presume that the early successful settlers of the Deccan were the DLF, who survived on abundant palm trees in most of the scrub jungle fauna and flora, and subsequently on seasonal monsoon-driven wild crops such as pulses (Misra, 2001), rice in Tamil Nadu appears only during the megalithic period 300 BC. Southern India seems to have thus developed a shared linguistic, literary, and cultural tradition—Dravidian, predominantly non-Vedic and non-Sanskrit in origin (Fuller, 2006). This fits well with the equation of NRY HG L1-M20 as Dravidian marker with its autochthonous divergence and expansion. This HG is present in high frequency and diversity in Tamil Nadu (average 16%, DLF ~50%) and most of the Deccan, the Southern Dravidian territory, and is also present in low frequencies in Western frontiers and Central India. Interestingly, this clade is not seen in Central Dravidian speakers and its territory, such as Orissa. On the other hand an ancient, NRY HG H1-M52 lineages are the commonest in both Central and Southern India with highest frequency (32%) in Madhya Pradesh (Central India) and Dravidian land (Fig. 7.1). As it stands the Western Ghats and Central Indian rain forests seem to be the earliest home of these early migrants, giving rise to Dravidian cultural evolution. Whether it is autochthonous or originated somewhere else to blossom in Tamil Nadu is a question to be addressed.

Demic Expansion

The Dravidian is a language family and its origin is a highly contentious issue though not the cultural elements

(Krishnamurti, 2003; Trautmann, 2011). In the absence of archaeological evidences on early humans in Southern India, one may need to interpret it in the light of genetic data taking cultural elements into consideration. A demic expansion hypothesis of proto-Dravidian speakers who came from the Fertile Crescent to India was proposed originally based on the Nostratic hypothesis, a commonly held view that the proto-Dravidian language originated from the proto-Elamite language (McAlpin, 1981; Renfrew, 1996). As an evidence to this, the Neolithic archaeological finds at Mehrgarh in Afghanistan identifying a sedentary population in stratigraphy is quoted often (Kochhar, 2000). Similar archaeological evidences are yet to be identified in Southern India. Nonetheless, the absence of Vedic fire alters, rice, and horse relics in the excavations of early phases Harappan sites are taken as evidence of Dravidian spoken in the Indus valley civilization, though the writings of the Indus are still debatable (Allchin and Allchin, 1997; Kochhar, 2000; Mahadevan, 1977). The studies equating NRY HG L1-M20 to Dravidian (Sengupta et al., 2006) and the unique and high frequency and diversity of this clade in Tamil Nadu makes this land as a cradle of Dravidian civilization though not its origin. The absence of NRY HG L1-M20 in Central Dravidian speakers of Orissa suggests that the Dravidian linguistics or cultural elements were much prior to their origin. Brahui, the Westernmost region of Dravidian language-isolate speakers of Afghanistan/Pakistan share local Y chromosome profile with some specific lineages (Qamar et al., 2002) and thus suggesting this still is a relic of the early migration from the West that has been absorbed by later arrivals in large scales: presumably these migrants found the Brahui handy to communicate. Thus L1-M20 may still be a marker of demic expansion of this language for its people to blossom on the canopy, the Tamil Nadu. Whole genome studies indeed support a huge expansion of people in Southern India and dispersal towards the North and the East (Javed et al., 2012; Metspalu et al., 2011; Reich et al., 2009). The wetland farming was introduced into Tamil Nadu only during Chola period 300s BCE to 1279 CE, Southern Neolithic people in Karnataka has been dated around 2nd Century BCE. This period is the arrival of Indo-European-speaking people into Tamil Nadu to document Tamil Sangam the ancient literary period of Tamil language, 300 BC−200 AD, with a well-developed society.

The demic expansion and the arrival of the Central Asian gene pool need to be corroborated with the scenario described earlier. It is interesting to note that two waves of Pleistocene expansion took place in India between 50,000 and 37,000 ka (Shi et al., 2010; Underhill et al., 2001); a coalescence of various South Asian populations dates back to 36−46 ka (Wei et al., 2013). Worldwide human settlement history and genome-wide patterns of variations have supported this dispersal and serial founder effects from Africa toward the East (Li et al., 2008; Liu et al., 2006). These are in close agreement with archaeological and anthropological evidence (Mellars et al., 2013). This implies that an ancient Northern Indian expansion occurred without influencing the Southern Deccan, and the 7000 years of Mehrgarh and ~5000 years of Harappan as a well-organized stratified society with maritime trades with Egyptians and Romans must have been the pinnacle of this ancient civilization (Allchin and Allchin, 1997).

Settled Agriculture

Settled agriculture is considered a primary cause of the formation of families and extended families, demes-population groups, and the possession and inheritance of properties (Chaix et al., 2004). The Harappan, a city-state with well-established technology and maritime trade with the West, and with its city planning and architecture, disappeared without trace (Thapar, 1995). Nonetheless, the very successful Swat Pirak culture, with painted grey wares, is considered the origin of Vedic culture in India: be it arrival from Central Asia via the Hindu Kush ranges or autochthonous (Cavalli-Sforza, 1997; Kochhar, 2000; Sharma et al., 2009; Wells et al., 2001). The origin of this culture ~2500 BC and the purported absence of Vedic influence in this culture till the late Harappan phase (cf. Kochar, 2000) need to be looked at in the context of the recent genetic evidences of Y chromosome/male migrations that the marker for Indo-European language speakers in India, NRY HG R1a1-M17, might have arrived in India from North or West somewhere between 10 and 20,000 ybp. The wet land agricultural expansion in Indo-Gangetic doab marks the evolution of definite demes and stratified society with the torch bearers of Vedic rituals with this NRY HG R1a1-M17 or its derivatives yet to be identified. Studies on NRY HG R1a1-M17 in Europeans and South Asians have shown a deep coancestry predating mid-Holocene period (~10,000 ybp) (Underhill et al., 2010). Our study on the geospatial pattern of skin color allele SLC24A5 reflects a strong influence of language, geography, and demographic history of the populations, and further, sequencing 11.74 kb of 95 individuals worldwide has revealed the monophyletic nature of rs1426654-A alleles in South Asian and West Eurasian populations with a coalescence date at 22−28 ka (Basu Mallick et al., 2013). The study further revealed that this gene has also been a target for positive selection in Europe, the Middle East, Central Asia, Pakistan, and North India but not in South India. The claim that R1a1-M17 clade of India is autochthonous in origin (Sharma et al., 2009) can best be interpreted by an ancient seeding of R1a1 ancestral allele through the mountainous ranges of Swat Pirak culture, followed by new mutations and expansion of its derivatives in Northwestern India,

and crisscross population movements through Kyber and Bolan passes, hence a high diversity identified in this study. The higher social tiers of present-day Northern Indian populations starting from Gujarat to Bengal including the Brahmins, the torch bearers of Vedic culture sans the tribal populations, might be the descendants of this expansion. It is the demic expansion and the dispersal of wetland irrigation and Paddy cultivation that trickled down from the Indo-Gangetic doab, Orissa down through coastal Andhra Pradesh to Tamil Nadu and Pallava-Chola country, Cauvery, and other riverine belts during the post-Sangam period, 600−1000 AD that brought down these people to Tamil Nadu. The R1a1-M17 is a predominant and ubiquitous clade seen in Brahmins, artisan, and warrior populations of the whole of Northern and Northwest India and the Deccan, except the dry land farming Dravidian and tribal populations (ArunKumar et al., 2012b; Kavitha, 2008), of Dravidian and Austro-asiatic speaking belts. The arrival of this wetland farming in Tamil Nadu ushered in "Mutt" (religious congregation and community living) concepts, these religious centers being the link between the Brahman and the locals in cultivation and resource sharing (Champaklakshmi, 2001; Shastri, 1976). The male hegemony and patrilineal concept of family must have thus arrived from Central Asia (Chaix et al., 2004), through Northern India, since the early Chola society of Tamil Nadu was more female-centric (Karashima et al., 1978). The private land holdings appeared in Tamil Nadu only during the later and post-Chola period, with the male hegemony and patriarchal ethos as in the case of Kazakhstan (Chaix et al., 2007). Thus the wetland farming communities, Vellala (artisans and farmers), Kar Katha Vellala of Chola country, Saiva Pillaimars of Pandiya country, and Kongu Vellala of Chera country played crucial roles in the agricultural development and local polity and power.

The genomic identity of these people in the context of the Central Asian, East European, and Northern Indian populations will tell the recent history of India better. Nonetheless, this was the golden period of Tamil Nadu, when Raja Raja Chola conquered the Himalayas and had maritime trade not only with the Egyptians and Romans on the West, but also with Indochina and Bali, Indonesia, establishing the Hindu culture in these places. However, has not impacted the whole of Tamil Nadu, except the Cauvery and other river belts. The societal stratification identified by disparate gene pools that was laid down 7000 ybp itself has not become similar by these later migrations and criss-cross population movements, until date (ArunKumar et al., 2012b). The subsistence-based demes living in various niches was further crystallized by cultural evolution leading to the caste formation, the last in recent times $<$2000 years further maintaining the distances of these gene pools.

Culture, an Isolation Parameter

Culture as a factor of isolation is supported by the picture we get from epigraphic records of Tamil Nadu. The societies in early Chola period ($\sim$800 AD) were more female-centric as their names appear in inscriptions, and male names appear only during the later Chola period ($\sim$1200 AD) (Karashima et al., 1978; Subbarayalu, 2012). It was during this period the Brahmadeya concept was introduced. Under this model the Brahmin settlements, called Agraharam of various temple cities and Seri, the earlier settlers living on the periphery of these settlements appeared in Tamil Nadu (Champaklakshmi, 2001). This temple-centric and ritual-driven society lead to the state cultivation of crops, community kitchens, etc. Various Mutts (religious sect heads and community living) controlled the water-taming technology and the resultant agriculture. The later migrant populations with water-taming technology settled amidst preexisting populations isolated or mingled to various degrees, reinforcing the societal stratification further by cultural elements and value systems. The Varna system and a color caste system were introduced, characterized by familial occupation crystallized with codified conduct and functions in the subdivided, hierarchical society. This, indeed, was reflected in the NRY chromosome composition of various stratified demes (castes and tribes) of Tamil Nadu. The initial settlements in various niches far apart from each other (100s of km) and expansion lead to geographical dispersal, and hence we could observe the coancestry of many demes as we described in the Southern Indian DLF populations such as Piramalai Kallar, Vanniyar, Nadar, Ezhava, and Thiyya, all with similar family, lifestyle, and subsistence (ArunKumar et al., 2012b; Kavitha, 2008)—whereas in the case of Brahmin- and Vellala-related communities, they were closer to each other and stand isolated from the rest of the population irrespective of the state from where they live now (ArunKumar 2012; ArunKumar et al., 2012b). The genetic landscape thus fits well with an ancient demic expansion with dry land cultivation of this L1 gene pool, and a later migration of R1a1 people, with wet land agriculture technology. Presumably the religion was incidental and the Vedic culture made them stay isolated at the NRY level through the anuloma and prathiloma concepts, resulting in many Brahmin populations of India absorbing early settled female gene pools into their fold (Majumder, 2008; Shastri, 1976). The lifestyle of the Sangam period explains the religious harmony of that period with Buddhism, Jainism, and a more appealing Hinduism—Bakthi movements, Vaishnava philosophy, and birth reincarnation. The urban centers and sea ports such as Poompuhar, Vanchi, and Korkai of the East and West coasts of the lower Deccan traded pearls, peacocks, sandalwood, teak,

ebony, and pepper with Romans, known as "Yavanars" (Thapar, 1995). The affluent, urban life style of this period is described at length in great epics "Silappathikaram" and "Manikegalai," the Sangam literature (~2000 ybp). The advent of land holdings presumably in combination with these religious thoughts lead to further crystallization of various demes. Family, the basic unit of a modern society with patriarchy and monogamy, came into vogue in these modern populations, though many tribal populations even today show varied cultures, values, and belief systems in marriage and lifestyle. As on date in a caste characterized by endogamy and clan exogamy, many times the clans, paternal lineages of a given caste have been drawn from various directions. Higher the status in social hierarchy, hegemony, and affluence, was strong their belief system (Pitchappan et al., unpublished). These pointers indicate that the caste system in Tamil Nadu (Sanghvi et al., 1981) is very young, only ~2000 years, and it reinforced the already structured Tamil society. A similar picture is emerging in many parts of the country as well (the Genographic India data). These divergent gene pools, living sympatrically isolated in a given geography may not be equally susceptible to a given epidemic as we discuss in the next section.

IMPLICATIONS IN HEALTH AND DISEASE

Not All the Infected Develop the Disease

It is common knowledge that every body in the population does not contract a flu or cold, and this is by virtue of the individual genetic composition: immunogenome. We have shown enormous genetic distances between various caste groups and populations of India (Pitchappan, 2002). Thus not all the castes may be susceptible to a given epidemic to the same degree. A classical example is the correlation between HIV-infected "long term nonprogressors" and HLA B57 allele that is present only in select populations/castes of India and not in all (Rajasekar et al., 1987; Jagannathan et al., 2011; Pitchappan, 2015). With the advent of germ theory, all the infections are considered as the product of an infectious agent, virus, or bacteria. We now know that in many instances a disease is not directly caused by the concerned bacteria/virus itself, rather it is the host reaction, be it immune response (HIV), biochemical imbalance (diabetes), or the germ-induced pathology (leprosy). Many times the immunopathological response to the antigenic constituents (proteins, breakdown products) results in the disease state, such as nephritis and multiple sclerosis (MS) (Cardona and Ivanyi, 2011). Major loci that harbor many of these genes involved in antigen presentation, immunological, and inflammatory pathways are located in the MHC region in c6p21.3: allelic polymorphism is the highest in some of these loci (Trowsdale and Knight, 2013) (Table 7.1). The greater the diversity of a given locus, the greater it is generally believed that it is involved in natural selection processes (Cavalli-Sforza, 2007). In spite of these great discoveries and better understanding of these diseases, many of them defy solution and better understanding (HIV, leprosy, MS, diabetes, etc.). Diseases other than the monogenic, and many times complex and chronic disease are polygenic and multifactorial. One will not thus get a disease that easily. If we invoke six different loci involved in a disease process, the probability of obtaining such combination is one in million—similar to winning the lottery. But within a family among two given sibships, it is of the order of one or two digits depending on the linkage of these loci on the chromosome and among the parents. These are exemplified by the fact that not all the intimate contacts of leprosy patients sharing the same domicile and nutrition develop the disease during their lifetime but the concordance rate of leprosy and TB manifestation is ~85% in identical twins (Chakravartti and Vogel, 1973; van der Eijk et al., 2007). This is an indicator that host genetics is more important in disease manifestation rather than the infectious agent *per se*. This assumes greater significance at the "ethnic," population, and continental level. By virtue of the founder effect, inbreeding, and endogamy, even many six loci MHC haplotypes are unique to given populations (Balakrishnan et al., 1996) and one may not expect all of them to behave in a similar fashion to an infection.

Lotus and Cactus Model

We call this the "Lotus and Cactus model" (Pitchappan, 2015b): a lotus grows in a pond and a cactus in a desert: but not the other way. Thus a TB patient's lung is an ideal "nutrient broth" for the TB bacilli to grow. Our whole Genome Scan using microsatellite markers in 256 affected sib pair from India has identified a handful of markers in the genome predisposing for leprosy (Siddiqui et al., 2001; Tosh et al., 2002). Our study has been replicated in Vietnamese cohorts: a rare event that two genome scans on entirely different cohorts are concordant (Mira et al., 2003). Furthermore, the utility of disparate demes in disease studies have been demonstrated time and again in leprosy. Genome scans that proved positive with c10p13 in our study did not hold for another marker in c20: while c20 association is valid in Tamil Nadu samples, it did not show any association in patients from Andhra Pradesh (Tosh et al., 2002). Similar observations have been made in psoriasis, TB (Pitchappan, 2002; Pitchappan et al., 1989), and cardiovascular diseases (unpublished). In these cases the relative risks increased multifold on stratification of samples based on caste matched case controls.

TABLE 7.1 Allelic (Sequence) Polymorphism of Select Major Histocompatibility Loci in c6-p21.3, as of July 2015: The Phenotype (Protein Level) Polymorphisms are Also Listed (Ref: www.hla.alleles.org/nomenclature/stats.html)

HLA Class I						
Gene	A	B	C	E	F	G
Alleles	3192	3977	2740	17	22	50
Proteins	2245	2938	1941	6	4	16
Nulls	150	128	89	1	0	2

HLA Class II										
Gene	DRA	DRB	DQA1	DQB1	DPA1	DPB1	DMA	DMB	DOA	DOB
Alleles	7	1868	54	807	40	550	7	13	12	13
Proteins	2	1364	32	539	20	447	4	7	3	5
Nulls	0	45	1	20	0	15	0	0	1	0

HLA Class II - DRB Alleles									
Gene	DRB1	DRB2	DRB3	DRB4	DRB5	DRB6	DRB7	DRB8	DRB9
Alleles	1764	1	59	16	21	3	2	1	1
Proteins	1290	0	47	9	18	0	0	0	0
Nulls	39	0	1	3	2	0	0	0	0

Other Non-HLA Genes				
Gene	MICA	MICB	TAP1	TAP2
Alleles	102	41	12	12
Proteins	80	27	6	5
Nulls	2	2	1	0

Pharmacogenomics

There are many studies in recent times showing an unequivocal association of select genes with hypersensitivity to select drugs. One such widely known is Abacavir, an antiretroviral drug commonly used to treat AIDS patients, and patients with HLA-B*57:01 develop severe adverse reactions. Another sister clade of this HLA, viz B*58:01 has on the other hand been shown to cause severe cutaneous adverse reactions with an allopurinol treatment for gout patients. Hence the clinics have started testing HLA B*57 and *58 status before prescribing these drugs. Nonetheless, the major catch in this approach is the frequency of these alleles in various populations. It is known that HIV infected patients with HLA B*57 normally turn into long-term nonprogressors (LTNP) and in India too these patients show good CD4 count and may stay healthy for a long time without progressing toward AIDS (Jagannathan et al., 2011). HLA B17, particularly its split, B*57, is one of the common alleles in India to be called a Telugu haplotype in a Durban, South African study, as early as 1979 (Hammond et al., 1979). This allele and its haplotype HLA A1-B17 is present only in certain populations of India and, again, not all the castes of a state (Pitchappan, 2015a). In order to put these tools to effective use one may need to map the immunogenome of a country. The "ethnic" diversity, though, could pose a problem to clinicians and epidemiologists; it is a boon to geneticists to unravel the mysteries of disease susceptibility. Many times epidemiologists look at the variables known to them only to forget the host and pathogen genomic diversities.

Survival Dictum

The MHC haplotypes of various world populations are very disparate, and this is true with Indian castes as well. When a polygenic and multifactorial etiopathology is invoked for a disease, the combination of genome and markers involved

need to be looked at as we know that these may be different from one population to another. The genomic diversity at the level of host and parasite poses a greater hurdle in vaccine development (Walker and McMichael, 2012). In the process of coevolution of a host and parasite over a period of time, this is not surprising. An elegant study on the correlates of genomic deletions in the TB bacilli and the extant of lung lesions in TB patinets revealed greater the genomic deletions in the pathogen, was less extensive the lung lesions—that means a less severe disease (Gagneux and Small, 2007). This has great relevance in high endemic areas; it is important what bug (virulent vs less virulent; more deleted vs less deleted) infects a child when born in to this world. If less virulent TB bacilli infects the baby first, the chances of not developing a clinical disease and becoming immune is greater. If a virulent, "more infectious" bug infects, the child might develop clinical TB. This is the rationale of administering the TB vaccine (BCG) soon after birth. This milieu of epidemiology is ever changing and contemporary and this is all the more important in deciphering the diseases; the epidemiology of Chengleput now is not the same as that of 40 years ago when BCG vaccine trial was conducted. This is true for viral infections as well: in many HIV-infected individuals the infections do not progress toward disease that easily. Individuals with HLA B57 infected with HIV in general become an long term non-progressor (LTNP), and their CD4 counts are normal for a long time (Jagannathan et al., 2011). These patients with HLA B57 are known to develop escape mutants, thus evading attack by cytotoxic T cells of the immune system and generated to kill the virus infected CD4 cells (Leslie et al., 2004). In terms of epidemiology, these apparently healthy "carriers" stay in the population for a while, thus infecting more partners (Pitchappan, 2015a).

Recent genomic studies also conform to the findings on classical genetics. Modeling single nucleotide polymorphism (SNP) haplotype diversities obtained through studying 600,000 SNPs suggests that both the Indian ancestry components, one shared with West Asia and the Caucasus and the other restricted to South Asia accounting for more than 50% of the ancestry in Indian populations are much older than the purported Indo-Aryan invasion 3500 ybp. Many candidate genes of positive selection have also been identified in India. Two of these, *MSTN* and *DOK5*, both have potential implications in lipid metabolism and the etiology of type 2 diabetes (Metspalu et al., 2011). Positive selection operating on KIR polymorphisms have selected natural killer cells expressing the dominant KIR3DL1 at high frequency and high surface density, respond strongly to cells perturbed in Bw4 expression. Among the five binding-site motifs residues of KIR, D0 new splits are more prevalent in Europeans and South Asians markedly increasing their functional 3DL1 diversity, beyond that defined by D1−D2 motifs alone (Norman et al., 2007). A recent collaborative genome-wide association study of large international HIV cohorts, using 1.3 million SNPs strewn over all the chromosomes, has demonstrated the utility of such stratification and clustering of samples into ethnic groups, as of European, Hispanic, and African-American ancestry based on PCA, to find the real meaning of identified associations and point out the purpose of rigorously controlling for ethnicity (Carrington and Walker, 2012). We have shown the importance of such stratification and matching the case control for castes in ancient gene pools like India (Pitchappan et al., 2008; Ravikumar et al., 1999), wherein geography and languages correlate to the whole genome and also Y chromosomes (ArunKumar et al., 2015a; Pitchappan, 2008). Studies that do not match case controls for ethnicity and other demographic variables may not identify the real association with the genes.

INDIA: GRANDEST EXPERIMENT OF NATURE

Dobzhansky, who visited India during the 1960s (Prof. Krishnaswamy (late) personal communication) was curious to understand the caste system in Southern India, known for its inbreeding and endogamy. In many of his writings Dobzhansky (1973) argues about the development of excellence and purification, if any, by such methods. He commented "Caste system in India is the greatest biological experiment ever done on *Homo sapiens*" (Sanghvi et al., 1981). India is no less true to the words of Dobzhansky or Lalit Sanghvi, author of the B squared method of genetic distance, a mathematician turned genetic epidemiologist and a postdoctoral student of Dobzhansky's and Iravathi Karve's—one of the doyen in social anthropology from India, Deccan College, Pune—who were the first to appreciate the evolutionary implications of such diverse gene pool. The enormous diversity and distances identified between the various social groups of India serve as ideal models to study the role of these disparate gene pools in health and disease status. The Genographic study and the genome scan studies on India that have been carried out open up new avenues of research in genetic epidemiology and community genetics. The evolution and implications of genomic diversity of humankind in India is thus indeed Nature's grandest biological experimentation.

CONCLUSION

The enormous genetic diversity observed in India is a sequela of ancient migrations and settlements in various niches, and autochthonous expansion with incidental language developments, all determined primarily by the mode of subsistence. This initial stratification crystallized

into caste system with the advent of settled agriculture and the resultant patriarchal society. By virtue of their origin, migration, divergence and settlements, and the resultant genetic composition, all of these demes living sympatrically isolated in a given niche/State may not be equally susceptible to a given epidemic or disease. The host genome and MHC determines whether all the infected develop the disease or not—an evolutionary way of thinking. One has to explore this experimentation to unravel the mysteries of the challenging diseases. This is very much applicable in this genomic era as well.

ACKNOWLEDGMENTS

Pitchappan thanks various funding agencies through the past four decades that helped with this conceptual framework. These include European Commission, Wellcome Trust-UK, INSERM-France, Government of India funding agencies viz. DST, DBT, ICMR and The Genographic Project funded by The National Geographic Society, IBM & Tedd Wait Family Foundation—The United States. Pitchappan also acknowledges the contributions of all his students in synthesizing this hypothesis by their contribution at various levels; the notable few testing these hypotheses at various levels were Drs. Brahmajothi, Balakrishnan, Shanmugalakshmi, Dheenadhayalan, Vani, Kavitha, and Arunkumar. We acknowledge Chettinad Academy of Research and Education, Kelampakkam and Sastra University, Thirumalaisamudram for their support and vision.

REFERENCES

Allchin, B., Allchin, F.R., 1997. Origins of a Civilization: The Prehistory and Early Archaeology of South Asia. Viking, New Delhi.

Ambedkar, B.R., 1956. States Reorganisation Act 1956 (New Delhi).

Arunkumar, G., Arun, V., Syama, A., Kavitha, V., Pitchappan, R., 2012a. Genomic perspective of peopling and languages of the Indian Subcontinent. In: Kumar, D. (Ed.), Genomics and Health in the Developing World. Oxford University Press, Oxford, p. xxxiii, 1501 p.

ArunKumar, G., Soria-Hernanz, D.F., Kavitha, V.J., Arun, V.S., Syama, A., Ashokan, K.S., Gandhirajan, K.T., Vijayakumar, K., Narayanan, M., Jayalakshmi, M., Ziegle, J.S., Royyuru, A.K., Parida, L., Wells, R.S., Renfrew, C., Schurr, T.G., Smith, C.T., Platt, D.E., Pitchappan, R., Consortium, T.G., 2012b. Population differentiation of southern Indian male lineages correlates with agricultural expansions predating the caste system. PLoS One 7 (11), e50269. http://dx.doi.org/10.1371/journal.pone.0050269.

ArunKumar, G., Tatarinova, T.V., Duty, J., Rollo, D., Syama, A., Arun, V.S., Kavitha, V.J., Triska, P., Greenspan, B., Wells, R.S., Pitchappan, R., 2015a. Genome-wide signatures of male-mediated migration shaping the Indian gene pool. Journal of Human Genetics. http://dx.doi.org/10.1038/jhg.2015.51, jhg201551 [pii].

Arunkumar, G., Wei, L.-H., Kavitha, V.J., Syama, A., Arun, V.S., Sathua, S., Sahoo, R., Balakrishnan, R., Riba, T., Chakravarthy, J., Chaudhury, B., Panda, P.K., Das, P., Nayak, P.K., Li, H., Pitchappan, R., The Genographic Consortium, 2015b. A late Neolithic expansion of Y chromosomal haplogroup O2a1-M95 from east to west. Journal of Systematics and Evolution. http://dx.doi.org/10.1111/jse.12147, n/a-n/a.

ArunKumar, G., 2012. Studies on the NRY and mtDNA Genomic Diversity of Selected Indian Populations Carrying the NRY Haplogroups R and O: Deciphering the Early Settlement of Austro-Asiatic and Indo-European Speakers of India. Madurai Kamaraj University.

Atkinson, Q.D., 2011. Phonemic diversity supports a serial founder effect model of language expansion from Africa. Science 332, 346–349. http://dx.doi.org/10.1126/science.1199295, 332/6027/346 [pii].

Balakrishnan, K., Pitchappan, R.M., Suzuki, K., Kumar, U.S., Santhakumari, R., Tokunaga, K., 1996. HLA affinities of Iyers, a Brahmin population of Tamil Nadu, South India. Human Biology 68, 523–537.

Balanovsky, O., Dibirova, K., Dybo, A., Mudrak, O., Frolova, S., Pocheshkhova, E., Haber, M., Platt, D., Schurr, T., Haak, W., Kuznetsova, M., Radzhabov, M., Balaganskaya, O., Romanov, A., Zakharova, T., Soria Hernanz, D.F., Zalloua, P., Koshel, S., Ruhlen, M., Renfrew, C., Wells, R.S., Tyler-Smith, C., Balanovska, E., 2011. Parallel evolution of genes and languages in the Caucasus region. Molecular Biology and Evolution 28, 2905–2920. http://dx.doi.org/10.1093/molbev/msr126.

Bamshad, M., Kivisild, T., Watkins, W.S., Dixon, M.E., Ricker, C.E., Rao, B.B., Naidu, J.M., Prasad, B.V., Reddy, P.G., Rasanayagam, A., Papiha, S.S., Villems, R., Redd, A.J., Hammer, M.F., Nguyen, S.V., Carroll, M.L., Batzer, M.A., Jorde, L.B., 2001. Genetic evidence on the origins of Indian caste populations. Genome Research 11, 994–1004. http://dx.doi.org/10.1101/gr.173301.

Basu, A., Mukherjee, N., Roy, S., Sengupta, S., Banerjee, S., Chakraborty, M., Dey, B., Roy, M., Roy, B., Bhattacharyya, N.P., Roychoudhury, S., Majumder, P.P., 2003. Ethnic India: a genomic view, with special reference to peopling and structure. Genome Research 13, 2277–2290. http://dx.doi.org/10.1101/gr.1413403.

Basu Mallick, C., Iliescu, F.M., Mols, M., Hill, S., Tamang, R., Chaubey, G., Goto, R., Ho, S.Y., Gallego Romero, I., Crivellaro, F., Hudjashov, G., Rai, N., Metspalu, M., Mascie-Taylor, C.G., Pitchappan, R., Singh, L., Mirazon-Lahr, M., Thangaraj, K., Villems, R., Kivisild, T., 2013. The light skin allele of SLC24A5 in South Asians and Europeans shares identity by descent. PLoS Genetics 9, e1003912. http://dx.doi.org/10.1371/journal.pgen.1003912, PGENETICS-D-13-01047 [pii].

Bellwood, P.S., Renfrew, C., McDonald Institute for Archaeological Research, 2002. Examining the Farming/Language Dispersal Hypothesis. McDonald Institute for Archaeological Research. Distributed by Oxbow Books, Cambridge, UK Oxford.

Brahmajothi, V., Pitchappan, R.M., Kakkanaiah, V.N., Sashidhar, M., Rajaram, K., Ramu, S., Palanimurugan, K., Paramasivan, C.N., Prabhakar, R., 1991. Association of pulmonary tuberculosis and HLA in south India. Tubercle 72, 123–132.

Cardona, P.J., Ivanyi, J., 2011. The secret trumps, impelling the pathogenicity of tubercle bacilli. Enfermedades Infecciosas y Microbiología Clínica 29 (Suppl. 1), 14–19. http://dx.doi.org/10.1016/S0213-005X(11)70013-1, S0213-005X(11)70013-1 [pii].

Carrington, M., Walker, B.D., 2012. Immunogenetics of spontaneous control of HIV. Annual Review of Medicine 63, 131–145. http://dx.doi.org/10.1146/annurev-med-062909-130018.

Cavalli-Sforza, L.L., Menozzi, P., Piazza, A., 1994. The History and Geography of Human Genes. Princeton University Press, Princeton, NJ.

Cavalli-Sforza, L.L., 1997. Genes, peoples, and languages. Proceedings of the National Academy of Sciences of the United States of America 94, 7719–7724.

Cavalli-Sforza, L.L., 2007. Human evolution and its relevance for genetic epidemiology. Annual Review of Genomics and Human Genetics 8, 1–15. http://dx.doi.org/10.1146/annurev.genom.8.080706.092403.

Chaix, R., Austerlitz, F., Khegay, T., Jacquesson, S., Hammer, M.F., Heyer, E., Quintana-Murci, L., 2004. The genetic or mythical ancestry of descent groups: lessons from the Y chromosome. The American Journal of Human Genetics 75, 1113–1116. http://dx.doi.org/10.1086/425938, S0002-9297(07)60078-0 [pii].

Chaix, R., Quintana-Murci, L., Hegay, T., Hammer, M.F., Mobasher, Z., Austerlitz, F., Heyer, E., 2007. From social to genetic structures in central Asia. Current Biology 17, 43–48. http://dx.doi.org/10.1016/j.cub.2006.10.058, S0960-9822(06)02433-X [pii].

Chakravartti, M.R., Vogel, F., 1973. A Twin Study on Leprosy. G. Thieme.

Champaklakshmi, R., 2001. Reappraisal of a Brahmanical Institution: the Brahmadeya and its ramifications in early midieval South India. In: Hall, K.R. (Ed.), Structure and Society in Early South India: Essays in Honour of Noboru Karashima. Oxford University Press, Delhi, pp. 59–84.

Chaubey, G., Metspalu, M., Choi, Y., Magi, R., Romero, I.G., Soares, P., van Oven, M., Behar, D.M., Rootsi, S., Hudjashov, G., Mallick, C.B., Karmin, M., Nelis, M., Parik, J., Reddy, A.G., Metspalu, E., van Driem, G., Xue, Y., Tyler-Smith, C., Thangaraj, K., Singh, L., Remm, M., Richards, M.B., Lahr, M.M., Kayser, M., Villems, R., Kivisild, T., 2011. Population genetic structure in Indian Austroasiatic speakers: the role of landscape barriers and sex-specific admixture. Molecular Biology and Evolution 28, 1013–1024. http://dx.doi.org/10.1093/molbev/msq288, msq288 [pii]

Dobzhansky, T., 1973. Genetic Diversity and Human Equality. Basic Books, New York.

Fuller, D.Q., 2006. Agricultural origins and frontiers in South Asia: a working synthesis. Journal of World Prehistory 20, 1–86.

Fuller, D.Q., 2007. Non-human genetics, agricultural origins and historical linguistics in South Asia. In: Petraglia, M.D., Allchin, B. (Eds.), The Evolution and History of Human Populations in South Asia. Springer, Dordrecht, The Netherlands, pp. 393–443.

Gagneux, S., Small, P.M., 2007. Global phylogeography of *Mycobacterium tuberculosis* and implications for tuberculosis product development. The Lancet Infectious Diseases 7, 328–337. http://dx.doi.org/10.1016/S1473-3099(07)70108-1, S1473-3099(07)70108-1 [pii].

Hammond, M.G., Appadoo, B., Brain, P., 1979. HLA and cancer in South African Indians. Tissue Antigens 14, 296–302.

Higham, C.F.W., 2002. Languages and farming dispersals: Austroasiatic languages and rice cultivation. In: Bellwood, P., Renfrew, A.C. (Eds.), Examining the Farming/Language Dispersal Hypothesis. McDonald Institute, Cambridge, pp. 223–232.

Jagannathan, L., Chaturvedi, M., Satish, B., Satish, K.S., Desai, A., Subbakrishna, D.K., Satishchandra, P., Pitchappan, R., Balakrishnan, K., Kondaiah, P., Ravi, V., 2011. HLA-B57 and gender influence the occurrence of tuberculosis in HIV infected people of south India. Clinical and Developmental Immunology 2011, 549023. http://dx.doi.org/10.1155/2011/549023.

Javed, A., Mele, M., Pybus, M., Zalloua, P., Haber, M., Comas, D., Netea, M.G., Balanovsky, O., Balanovska, E., Jin, L., Yang, Y., Arunkumar, G., Pitchappan, R., Bertranpetit, J., Calafell, F., Parida, L., 2012. Recombination networks as genetic markers in a human variation study of the Old World. Human Genetics 131, 601–613. http://dx.doi.org/10.1007/s00439-011-1104-8.

Jayalakshmi, M., Kalyanaraman, N., Pitchappan, R., 2012. The genetics of leprosy in India. In: Kumar, D. (Ed.), Genomics and Health in the Developing World. Oxford University Press, Oxford, p. xxxiii, 1501 p.

Karashima, N., Subbarayalu, Y., Matsui, T., 1978. A Concordance of the Names in Cola Inscriptions. Sarvodaya Ilakkiya Pannai, Madurai.

Kavitha, V.J., 2008. Studies on the Genomic Diversity of Southern Indian Breeding Isolates. Madurai Kamaraj University.

Kivisild, T., Bamshad, M.J., Kaldma, K., Metspalu, M., Metspalu, E., Reidla, M., Laos, S., Parik, J., Watkins, W.S., Dixon, M.E., Papiha, S.S., Mastana, S.S., Mir, M.R., Ferak, V., Villems, R., 1999. Deep common ancestry of Indian and Western-Eurasian mitochondrial DNA lineages. Current Biology 9, 1331–1334, bb9v50 [pii].

Kochhar, R., 2000. The Vedic People: Their History and Geography. Orient Longman, New Delhi.

Krishnamurti, B., 2003. The Dravidian Languages. Cambridge University Press, Cambridge.

Kumar, V., Reddy, A.N., Babu, J.P., Rao, T.N., Langstieh, B.T., Thangaraj, K., Reddy, A.G., Singh, L., Reddy, B.M., 2007. Y-chromosome evidence suggests a common paternal heritage of Austro-Asiatic populations. BMC Evolutionary Biology 7, 47. http://dx.doi.org/10.1186/1471-2148-7-47, 1471-2148-7-47 [pii].

Leslie, A.J., Pfafferott, K.J., Chetty, P., Draenert, R., Addo, M.M., Feeney, M., Tang, Y., Holmes, E.C., Allen, T., Prado, J.G., Altfeld, M., Brander, C., Dixon, C., Ramduth, D., Jeena, P., Thomas, S.A., St John, A., Roach, T.A., Kupfer, B., Luzzi, G., Edwards, A., Taylor, G., Lyall, H., Tudor-Williams, G., Novelli, V., Martinez-Picado, J., Kiepiela, P., Walker, B.D., Goulder, P.J., March 2004. HIV evolution: CTL escape mutation and reversion after transmission. Nature Medicine 10 (3), 282–289. Epub 2004 Feb 8. pmid:14770175.

Li, J.Z., Absher, D.M., Tang, H., Southwick, A.M., Casto, A.M., Ramachandran, S., Cann, H.M., Barsh, G.S., Feldman, M., Cavalli-Sforza, L.L., Myers, R.M., 2008. Worldwide human relationships inferred from genome-wide patterns of variation. Science 319, 1100–1104. http://dx.doi.org/10.1126/science.1153717, 319/5866/1100 [pii].

Liu, H., Prugnolle, F., Manica, A., Balloux, F., 2006. A geographically explicit genetic model of worldwide human-settlement history. The American Journal of Human Genetics 79, 230–237. http://dx.doi.org/10.1086/505436, S0002-9297(07)63131-0 [pii].

Mahadevan, I., 1977. The Indus Script: Texts, Concordance, and Tables. Archaeological Survey of India, New Delhi.

Majumder, P.P., 1998. People of India: biological diversity and affinities. Evolutionary Anthropology 6, 100–110.

Majumder, P.P., 2008. Genomic inferences on peopling of south Asia. Current Opinion in Genetics & Development 18, 280–284. http://dx.doi.org/10.1016/j.gde.2008.07.003.

McAlpin, D.W., 1981. Proto-Elamo-Dravidian: the evidence and its implications. Transactions of the American Philosophical Society 71, 3–155.

McElreavey, K., Quintana-Murci, L., 2005. A population genetics perspective of the Indus Valley through uniparentally-inherited markers. Annals of Human Biology 32, 154–162. http://dx.doi.org/10.1080/03014460500076223, K74332955H187555 [pii].

Mellars, P., Gori, K.C., Carr, M., Soares, P.A., Richards, M.B., 2013. Genetic and archaeological perspectives on the initial modern human colonization of southern Asia. Proceedings of the National Academy of Sciences of the United States of America 110, 10699–10704. http://dx.doi.org/10.1073/pnas.1306043110, 1306043110 [pii].

Metspalu, M., Romero, I.G., Yunusbayev, B., Chaubey, G., Mallick, C.B., Hudjashov, G., Nelis, M., Magi, R., Metspalu, E., Remm, M., Pitchappan, R., Singh, L., Thangaraj, K., Villems, R., Kivisild, T., 2011. Shared and unique components of human population structure and genome-wide signals of positive selection in South Asia. The American Journal of Human Genetics 89, 731–744. http://dx.doi.org/10.1016/j.ajhg.2011.11.010, S0002-9297(11)00488-5 [pii].

Minstry of Tribal Affairs: GOI, 2015. Scheduled Tribes Data. http://tribal.nic.in/Content/STATISTICSDivision.aspx (accessed 09.08.15.).

Mira, M.T., Alcais, A., Van Thuc, N., Thai, V.H., Huong, N.T., Ba, N.N., Verner, A., Hudson, T.J., Abel, L., Schurr, E., 2003. Chromosome 6q25 is linked to susceptibility to leprosy in a Vietnamese population. Nature Genetics 33, 412–415. http://dx.doi.org/10.1038/ng1096, ng1096 [pii]

Misra, V.N., 2001. Prehistoric human colonization of India. Journal of Biosciences 26, 491–531.

Norman, P.J., Abi-Rached, L., Gendzekhadze, K., Korbel, D., Gleimer, M., Rowley, D., Bruno, D., Carrington, C.V., Chandanayingyong, D., Chang, Y.H., Crespi, C., Saruhan-Direskeneli, G., Fraser, P.A., Hameed, K., Kamkamidze, G., Koram, K.A., Layrisse, Z., Matamoros, N., Mila, J., Park, M.H., Pitchappan, R.M., Ramdath, D.D., Shiau, M.Y., Stephens, H.A., Struik, S., Verity, D.H., Vaughan, R.W., Tyan, D., Davis, R.W., Riley, E.M., Ronaghi, M., Parham, P., 2007. Unusual selection on the KIR3DL1/S1 natural killer cell receptor in Africans. Nature Genetics 39, 1092–1099. http://dx.doi.org/10.1038/ng2111, ng2111 [pii]

Pitchappan, R.M., Kakkanaiah, V.N., Rajashekar, R., Arulraj, N., Muthukkaruppan, V.R., 1984. HLA antigens in South India: I. Major groups of Tamil Nadu. Tissue Antigens 24, 190–196.

Pitchappan, R.M., Koteeswaran, A., Kakkaniah, V.N., Manickasundari, M., Rajaram, V., Muthuveeralakshmi, P., Mahendran, V., Brahmajothibai, V., 1989. HLA Bw57 and DR7 association with psoriasis vulgaris in south India. Tissue Antigens 34, 133–137.

Pitchappan, R.M., Balakrishnan, K., Sudarsen, V., Brahmajothi, V., Mahendran, V., Amalraj, S., Santhakumari, R., Vijayakumar, K., Sivalingam, P., Ramasamy, S., 1997. Sociobiology and HLA genetic polymorphism in hill tribes, the Irula of the Nilgiri hills and the Malayali of the Shevroy hills, south India. Human Biology 69, 59–74.

Pitchappan, R., Kavitha, V., Jayalakshmi, M., 2008. HLA genomic diversity of India and its implications in HIV pandemic. International Journal of Human Genetics 8, 143–153.

Pitchappan, R., 1988. Founder effects explain the distri- bution of the HLA A1-B17 but not the absence of the A1-B8 haplotypes in India. Journal of Genetics 67, 101–111.

Pitchappan, R.M., 2002. Castes, migrations, immunogenetics and infectious diseases in south India. Community Genetics 5, 157–161.

Pitchappan, R.M., 2008. Genomic implications of Dravidian cultural evolution. In: First Great Migrations of Peoples. UNESCO, Paris, pp. 60–67, 169-170,446.

Pitchappan, R., 2015a. Personalized medicine. Chettinad Health City Medical Journal 4, 2.

Pitchappan, R.M, 2015b. Not all the infected develop the disease – a "Lotus and Cactus" model. Infection, Genetics and Evolution. http://dx.doi.org/10.1016/j.meegid.2015.11.007.

Qamar, R., Ayub, Q., Mohyuddin, A., Helgason, A., Mazhar, K., Mansoor, A., Zerjal, T., Tyler-Smith, C., Mehdi, S.Q., 2002. Y-chromosomal DNA variation in Pakistan. The American Journal of Human Genetics 70, 1107–1124. http://dx.doi.org/10.1086/339929, S0002-9297(07)62507-5 [pii].

Quintana-Murci, L., Fellous, M., 2001. The human Y chromosome: the biological role of a "functional wasteland". Journal of Biomedicine and Biotechnology 1, 18–24. http://dx.doi.org/10.1155/S1110724301000080, S1110724301000080 [pii].

Rajalingam, R., Du, Z., Meenagh, A., Luo, L., Kavitha, V.J., Pavithra-Arulvani, R., Vidhyalakshmi, A., Sharma, S.K., Balazs, I., Reed, E.F., Pitchappan, R.M., Middleton, D., May 2008. Distinct diversity of KIR genes in three southern Indian populations: comparison with world populations revealed a link between KIR gene content and pre-historic human migrations. Immunogenetics 60 (5), 207–217. http://dx.doi.org/10.1007/s00251-008-0286-2, Epub 2008 Mar 28, pmid:18369612.

Rajasekar, R., Kakkanaiah, V.N., Pitchappan, R.M., 1987. HLA antigens in South India: II. Selected caste groups of Tamil Nadu. Tissue Antigens 30, 113–118.

Ramachandran, S., Deshpande, O., Roseman, C.C., Rosenberg, N.A., Feldman, M.W., Cavalli-Sforza, L.L., 2005. Support from the relationship of genetic and geographic distance in human populations for a serial founder effect originating in Africa. Proceedings of the National Academy of Sciences of the United States of America 102, 15942–15947. http://dx.doi.org/10.1073/pnas.0507611102, 0507611102 [pii].

Ravikumar, M., Dheenadhayalan, V., Rajaram, K., Lakshmi, S.S., Kumaran, P.P., Paramasivan, C.N., Balakrishnan, K., Pitchappan, R.M., 1999. Associations of HLA-DRB1, DQB1 and DPB1 alleles with pulmonary tuberculosis in south India. Tubercle and Lung Disease 79, 309–317, S0962847999902137 [pii].

Reich, D., Thangaraj, K., Patterson, N., Price, A.L., Singh, L., 2009. Reconstructing Indian population history. Nature 461, 489–494. http://dx.doi.org/10.1038/nature08365.

Renfrew, C., 1996. Language families and the spread of farming. In: Harris, D.R. (Ed.), The Origins and Spread of Agriculture and Pastoralism in Eurasia. Smithsonian Institution Press, Washington, DC, pp. 70–92.

Sahoo, S., Singh, A., Himabindu, G., Banerjee, J., Sitalaximi, T., Gaikwad, S., Trivedi, R., Endicott, P., Kivisild, T., Metspalu, M., Villems, R., Kashyap, V.K., 2006. A prehistory of Indian Y chromosomes: evaluating demic diffusion scenarios. Proceedings of the National Academy of Sciences of the United States of America 103, 843–848. http://dx.doi.org/10.1073/pnas.0507714103, 0507714103 [pii].

Sanghvi, L.D., Balakrishnan, V., Karve, I., 1981. Biology of the People of Tamil Nadu. Indian Society of Human Genetics and Indian Anthropological Society, Calcutta.

Semino, O., Magri, C., Benuzzi, G., Lin, A.A., Al-Zahery, N., Battaglia, V., Maccioni, L., Triantaphyllidis, C., Shen, P., Oefner, P.J., Zhivotovsky, L.A., King, R., Torroni, A., Cavalli-Sforza, L.L., Underhill, P.A., Santachiara-Benerecetti, A.S., 2004. Origin, diffusion, and differentiation of Y-chromosome haplogroups E and J: inferences on the neolithization of Europe and later migratory events in the Mediterranean area. The American Journal of Human Genetics 74, 1023–1034. http://dx.doi.org/10.1086/386295, S0002-9297(07)64366-3 [pii].

Sengupta, S., Zhivotovsky, L.A., King, R., Mehdi, S.Q., Edmonds, C.A., Chow, C.E., Lin, A.A., Mitra, M., Sil, S.K., Ramesh, A., Usha Rani, M.V., Thakur, C.M., Cavalli-Sforza, L.L., Majumder, P.P., Underhill, P.A., 2006. Polarity and temporality of high-resolution y-chromosome distributions in India identify both indigenous and

exogenous expansions and reveal minor genetic influence of Central Asian pastoralists. The American Journal of Human Genetics 78, 202–221. http://dx.doi.org/10.1086/499411, S0002-9297(07)62353-2 [pii].

Shanmugalakshmi, S., Balakrishnan, K., Manoharan, K., Pitchappan, R.M., 2003. HLA-DRB1*, -DQB1* in Piramalai Kallars and Yadhavas, two Dravidian-speaking castes of Tamil Nadu, South India. Tissue Antigens 61, 451–464, 061 [pii].

Sharma, S., Rai, E., Sharma, P., Jena, M., Singh, S., Darvishi, K., Bhat, A.K., Bhanwer, A.J., Tiwari, P.K., Bamezai, R.N., 2009. The Indian origin of paternal haplogroup R1a1(*) substantiates the autochthonous origin of Brahmins and the caste system. Journal of Human Genetics 54, 47–55. http://dx.doi.org/10.1038/jhg.2008.2, jhg20082 [pii]

Shastri, K.A.N., 1976. A History of South India: From Prehistoric Times to the Fall of Vijayanagar, fourth ed. Oxford University Press, Madras.

Shi, W., Ayub, Q., Vermeulen, M., Shao, R.G., Zuniga, S., van der Gaag, K., de Knijff, P., Kayser, M., Xue, Y., Tyler-Smith, C., 2010. A worldwide survey of human male demographic history based on Y-SNP and Y-STR data from the HGDP-CEPH populations. Molecular Biology and Evolution 27, 385–393. http://dx.doi.org/10.1093/molbev/msp243, msp243 [pii]

Siddiqui, M.R., Meisner, S., Tosh, K., Balakrishnan, K., Ghei, S., Fisher, S.E., Golding, M., Shanker Narayan, N.P., Sitaraman, T., Sengupta, U., Pitchappan, R., Hill, A.V., 2001. A major susceptibility locus for leprosy in India maps to chromosome 10p13. Nature Genetics 27, 439–441. http://dx.doi.org/10.1038/8695886958.

Southworth, F.C., 2005a. Linguistic Archaeology of South Asia. Routledge.

Southworth, F.C., 2005b. Prehistoric implications of the Dravidian element in the NIA lexicon with special reference to Marathi. International Journal of Dravidian Linguistics 34, 17–28.

Subbarayalu, Y., 2012. South India Under the Cholas. Oxford University Press, New Delhi, Oxford.

Thapar, R., 1995. The First Millennium B.C. in the Northern India (Bombay).

Tosh, K., Meisner, S., Siddiqui, M.R., Balakrishnan, K., Ghei, S., Golding, M., Sengupta, U., Pitchappan, R.M., Hill, A.V., 2002. A region of chromosome 20 is linked to leprosy susceptibility in a South Indian population. The Journal of Infectious Diseases 186, 1190–1193. http://dx.doi.org/10.1086/343806, JID020472 [pii].

Trautmann, T.R., 1981. Dravidian Kinship. Sage Publications Pvt Limited.

Trautmann, T.R., 2011. India: Brief History of a Civilization. Oxford University Press, New York.

Trivedi, R., Sahoo, S., Singh, A., Bindu, G.H., Banerjee, J., Tandon, M., Gaikwad, S., Rajkumar, R., Sitalaximi, T., Ashma, R., Chainy, G.B.N., Kashyap, V.K., 2008. Genetic imprints of pleistocene origin of Indian populations: a comprehensive phylogeographic sketch of Indian Y-chromosomes. Search Results International Journal of Human Genetics 8 (1–2), 97–118.

Trowsdale, J., Knight, J.C., 2013. Major histocompatibility complex genomics and human disease. Annual Review of Genomics and Human Genetics 14, 301–323. http://dx.doi.org/10.1146/annurev-genom-091212-153455.

Underhill, P.A., Passarino, G., Lin, A.A., Shen, P., Mirazon Lahr, M., Foley, R.A., Oefner, P.J., Cavalli-Sforza, L.L., 2001. The phylogeography of Y chromosome binary haplotypes and the origins of modern human populations. Annals of Human Genetics 65, 43–62, S0003480001008582 [pii].

Underhill, P.A., Myres, N.M., Rootsi, S., Metspalu, M., Zhivotovsky, L.A., King, R.J., Lin, A.A., Chow, C.E., Semino, O., Battaglia, V., Kutuev, I., Jarve, M., Chaubey, G., Ayub, Q., Mohyuddin, A., Mehdi, S.Q., Sengupta, S., Rogaev, E.I., Khusnutdinova, E.K., Pshenichnov, A., Balanovsky, O., Balanovska, E., Jeran, N., Augustin, D.H., Baldovic, M., Herrera, R.J., Thangaraj, K., Singh, V., Singh, L., Majumder, P., Rudan, P., Primorac, D., Villems, R., Kivisild, T., 2010. Separating the post-Glacial coancestry of European and Asian Y chromosomes within haplogroup R1a. European Journal of Human Genetics: EJHG 18, 479–484. http://dx.doi.org/10.1038/ejhg.2009.194.

van der Eijk, E.A., van de Vosse, E., Vandenbroucke, J.P., van Dissel, J.T., 2007. Heredity versus environment in tuberculosis in twins: the 1950s United Kingdom Prophit Survey Simonds and Comstock revisited. American Journal of Respiratory and Critical Care Medicine 176, 1281–1288. http://dx.doi.org/10.1164/rccm.200703-435OC, 200703-435OC [pii].

Walker, B., McMichael, A., 2012. The T-cell response to HIV. Cold Spring Harbor Perspectives in Medicine 2. http://dx.doi.org/10.1101/cshperspect.a007054, cshperspecta007054 [pii].

Watkins, W.S., Thara, R., Mowry, B.J., Zhang, Y., Witherspoon, D.J., Tolpinrud, W., Bamshad, M.J., Tirupati, S., Padmavati, R., Smith, H., Nancarrow, D., Filippich, C., Jorde, L.B., 2008. Genetic variation in South Indian castes: evidence from Y-chromosome, mitochondrial, and autosomal polymorphisms. BMC Genetics 9, 86. http://dx.doi.org/10.1186/1471-2156-9-86.

Wei, W., Ayub, Q., Chen, Y., McCarthy, S., Hou, Y., Carbone, I., Xue, Y., Tyler-Smith, C., 2013. A calibrated human Y-chromosomal phylogeny based on resequencing. Genome Research 23, 388–395. http://dx.doi.org/10.1101/gr.143198.112, gr143198.112 [pii].

Wells, R.S., Yuldasheva, N., Ruzibakiev, R., Underhill, P.A., Evseeva, I., Blue-Smith, J., Jin, L., Su, B., Pitchappan, R., Shanmugalakshmi, S., Balakrishnan, K., Read, M., Pearson, N.M., Zerjal, T., Webster, M.T., Zholoshvili, I., Jamarjashvili, E., Gambarov, S., Nikbin, B., Dostiev, A., Aknazarov, O., Zalloua, P., Tsoy, I., Kitaev, M., Mirrakhimov, M., Chariev, A., Bodmer, W.F., 2001. The Eurasian heartland: a continental perspective on Y-chromosome diversity. Proceedings of the National Academy of Sciences of the United States of America 98, 10244–10249.

Wood, M., 2007. The Story of India. BBC Books.

Zhong, H., Shi, H., Qi, X.B., Xiao, C.J., Jin, L., Ma, R.Z., Su, B., 2010. Global distribution of Y-chromosome haplogroup C reveals the prehistoric migration routes of African exodus and early settlement in East Asia. Journal of Human Genetics 55, 428–435. http://dx.doi.org/10.1038/jhg.2010.40, jhg201040 [pii]

Chapter 8

The Human Brain: Evolution and Distinctive Features

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INTRODUCTION

If we accept that cognition and behavior are functions of the brain, and if we accept that humans have evolved specialized cognitive and behavioral abilities, it follows that there are properties of the human brain that are uniquely or distinctively human, and that understanding those distinctive features is the proper goal of the scientific study of human brain evolution. For biologists of many stripes, this has been difficult to accept. Claims of human specialization smack of special pleading, amounting to denial of the continuity of species, an attempt to create a false barrier between humans and our closest relatives, the African great apes. The propinquity of humans to chimpanzees and bonobos has encouraged some to place them all in the human genus, *Homo* (Goodman et al., 1998), or, with similar logic, to regard humans as the "third chimpanzee" (Diamond, 1992). This attitude seems consistent with Darwin's view that the differences between humans and our closest relatives are matters of degree rather than kind (Darwin, 1871), a view echoed by Huxley in his treatment of human brain evolution (Huxley, 1863). For experimental neuroscientists, whose evolutionary commitments may not run very deep, human specializations can seem challenging as well, potentially calling into question the value of results obtained in model animals, be they monkeys, rodents, or fruit flies (Preuss and Robert, 2014).

Yet much of evolutionary biology is about barriers and differences, specifically, the reproductive barriers created by speciation and the differences that emerge between species after the establishment of reproductive isolation. Evolution is, after all, a theory of change, and species are, after all, defined by the features that make them different from each other. Claims about human specializations must ultimately stand or fall on the weight of evidence: One can always be mistaken about matters of fact, and one can make the more general error of failing to acknowledge that species other than humans have evolved their own special characteristics. But there is nothing necessarily unnatural or unbiological in proposing species-specific characteristics of the human brain—that is just what evolutionary biologists do for other species and other organ systems (Preuss, 2012a).

Of course, the validity of empirical claims about human brain evolution ultimately rests on the power of the investigative methods deployed and the quality of data obtained. For much of its history, the field has focused on the analysis of fossil brains, or more accurately, the impressions of brains left on the inner surface of the skull (endocasts). This paleoneurological approach provides information about when in evolutionary history changes took place in the size and shape of the brain, and sometimes about changes in cortical folding, although impressions of folds (gyri) and grooves (sulci) are rarely well preserved in large-brained animals. Unfortunately, endocasts provide us with no direct information about the neural structures and circuits that carry out brain functions. Inferring brain function from endocasts is like trying to understand how a computer works by studying the box it came in—not pointless, especially if that is all you have to work with (or if you think size is really all that matters, as some have), but less than ideal. Clearly, we would be greatly aided by having information about how the brains of humans resemble and differ from those of other living species—that is, comparative experimental studies of actual brains. Until recently, however, most of the experimental techniques

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available to neuroscientists were suited for use almost exclusively in experimental animal species, such as monkeys and rodents, because they require invasive and terminal procedures. These techniques include injecting chemicals into the brain to trace neuronal connections and inserting electrodes to record from or electrically stimulate neurons, and they usually end with the death of the subject, in order to determine where the tracers went or to confirm where the electrode was placed. While these provide very detailed information about model species, they cannot be used in species off-limits for invasive research, which include not only humans but, significantly, great apes as well.

Fortunately, we now have noninvasive neuroscientific methods that can provide data of a quality often approaching, and for some purposes exceeding, that of traditional invasive methods (Preuss, 2010; Rilling, 2008). Prominent among these are the different neuroimaging modalities, mainly different varieties of magnetic resonance imaging (MRI). There are MRI-based methods for documenting brain morphology, for mapping myelin density (which is useful for making cortical maps), and for tracking connectional pathways through white matter. Connectivity studies, employing diffusion-weighted or diffusion-tensor imaging (DWI, DTI), are especially important, given that the functions of brain regions depend on their connections. There are also functional MRI techniques, which measure regional brain activity levels. These include task-based paradigms, where one compares activity in different behavioral conditions, and "resting-state" paradigms, used to identify brain regions that show correlated patterns of activity or "functional connectivity" (in contrast to the structural connectivity evaluated with DWI). Not surprisingly, structures that are functionally connected tend to be structurally connected, although the relationship is not perfect. The virtue of these techniques, from the standpoint of studying human evolution, is that they can be used to directly study and compare humans, great apes, and other nonhuman primates. The structural techniques can even be used with brains acquired post-mortem. An additional set of methods that has been brought to bear on questions of brain evolution comes from comparative molecular biology, including techniques from genomics, proteomics, and related fields. As with the neuroimaging techniques, these do not require invasive techniques, and so are ideal for comparative studies.

Although the application of these techniques for studying human brain evolution, beginning in earnest in the 1990s, has greatly improved the research situation, there are still serious obstacles. By definition, human specializations are features of organization that evolved in our lineage after it separated from the lineages leading to our closest relatives, now generally considered to be the chimpanzee-bonobo lineage (Figs. 8.1 and 8.2). Logically, therefore, a candidate human specialization must be present in the human lineage, but absent in the chimpanzee-bonobo lineage. Of course, a mere *difference* between humans and chimpanzees could have resulted from a change in the chimpanzee-bonobo lineage, rather than the human lineage. For this reason, we need "outgroup" information—data from other closely related groups to estimate what the human-chimp ancestor was like. Ideally, we would also have information from gorillas, orangutans, gibbons, and Old World monkeys (such as macaques)—in that order of importance (Fig. 8.1).

In practice, we are far from the ideal. Currently, the nonhuman primates for which we have the most information are macaque monkeys, and thanks to the imaging revolution, our knowledge of human brain organization is rapidly growing. But access to a critical resource—the apes themselves—has been sharply reduced in recent years. We have some information about chimpanzees, but very little about the other apes. This places serious limitations on the quality of inferences we can make about human brain specializations. Certainly, we can say quite a bit about the similarities and differences between humans and macaques, and while these are useful and suggestive, they do not paint a very accurate or complete picture of human brain evolution. Suppose, for example, that one were to identify corresponding (homologous) brain areas in humans and macaques that differ to some degree in their functional properties (a number of such instances will be discussed later in this chapter). With information only from humans and macaques, we could not say whether the difference arose in the human lineage or the macaque lineage. And if it arose in the human lineage, it might have occurred after the human-chimpanzee split, in which case it would be a human specialization, or prior to it, in which case it would be an ape-human (hominoid) specialization. In some cases, one can plausibly (if not definitively) attribute changes to the human side of the macaque-human split, such as the tool-selective properties of the anterior inferior parietal lobule of humans compared to its macaque homologue (Peeters et al., 2009), but can we be sure chimpanzees do not share that specialization? In general, the safest attributions are probably those that involve major changes in the size of a structure, given the enormous overall size of the human brain. Yet even those inferences must be considered highly provisional in lieu of appropriate comparative evidence.

The following review of human brain evolution is necessarily selective, given space constraints. I focus on the cortex, which is the part of the brain about which the most data are available, reflecting the generally held view that the cortex is where most of the action occurred in human brain evolution, although it is certainly not the only brain region modified in human evolution. In addition, I emphasize comparative studies over paleoneurology, not

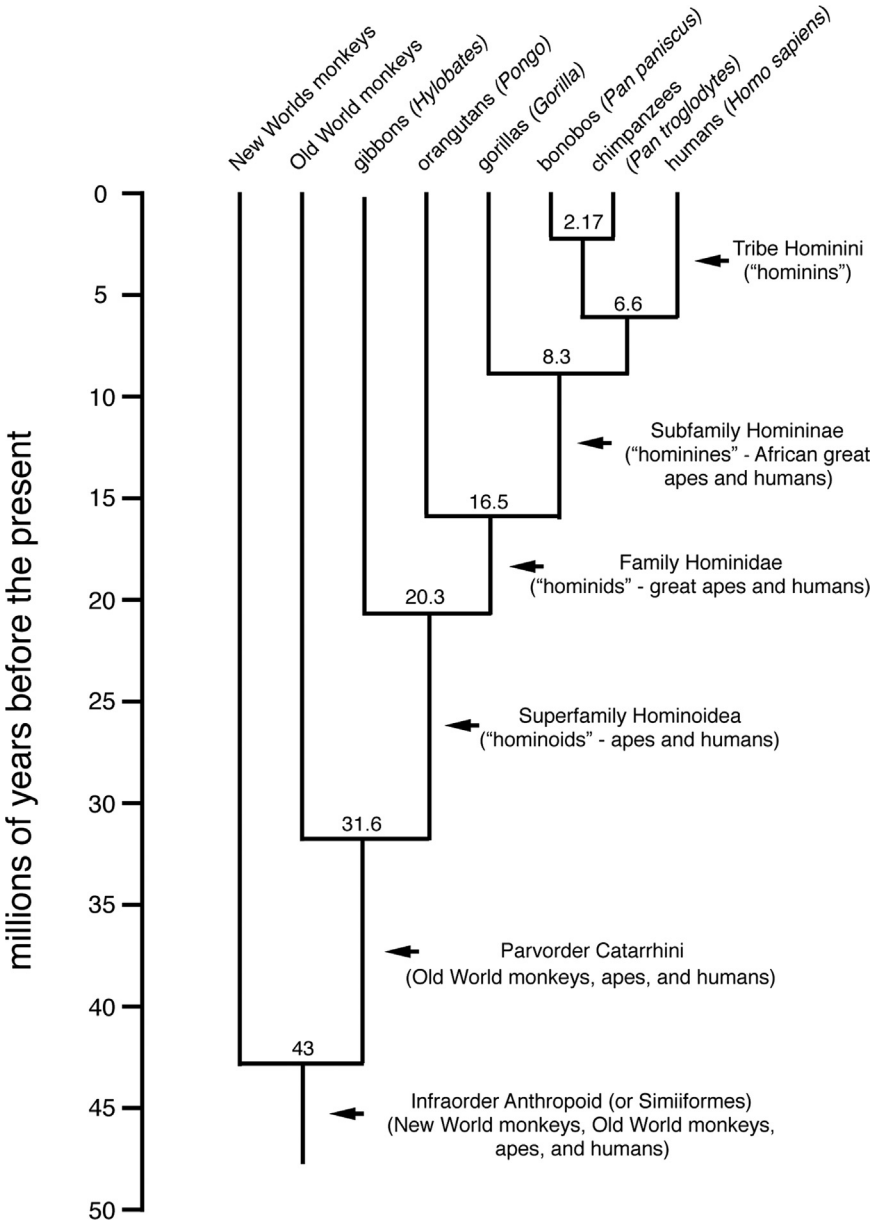

FIGURE 8.1 Phylogeny and taxonomy of the anthropoid primates. Branching orders and times are from Perelman et al. (2011). Branching time estimates vary between studies; most current estimates of the human-chimpanzee divergence fall between 5 and 8 Ma. The hominoid taxonomy is from de Sousa and Wood (2007).

only because I am more familiar with comparative research but also because it speaks more directly to changes in the internal organization of the brain and thus bears more directly on functional changes. I also briefly review some results from comparative genomic and molecular biological studies that are especially relevant to human brain evolution. In all these fields, I prioritize studies that include chimpanzees, as well as humans, for reasons outlined above. Finally, I emphasize results that speak to general principles, rather than trying to cover the literature comprehensively.

This is very much my own view of human brain evolution, and there are certainly others. In fact, a number of books and reviews on this subject have been published in recent years, in which you will find coverage of issues not dealt with here, as well as points of view that are sometimes in accord with my own, and sometimes at variance with them (eg, Allen, 2009; Cohen, 2010; de Sousa and Cunha, 2012; Falk, 2015; Gazzaniga, 2008; Holloway, 2008; Kaas and Preuss, 2013; Passingham, 2008; Premack, 2010; Rilling and Stout, 2014; Schoenemann, 2006; Sherwood et al., 2008).

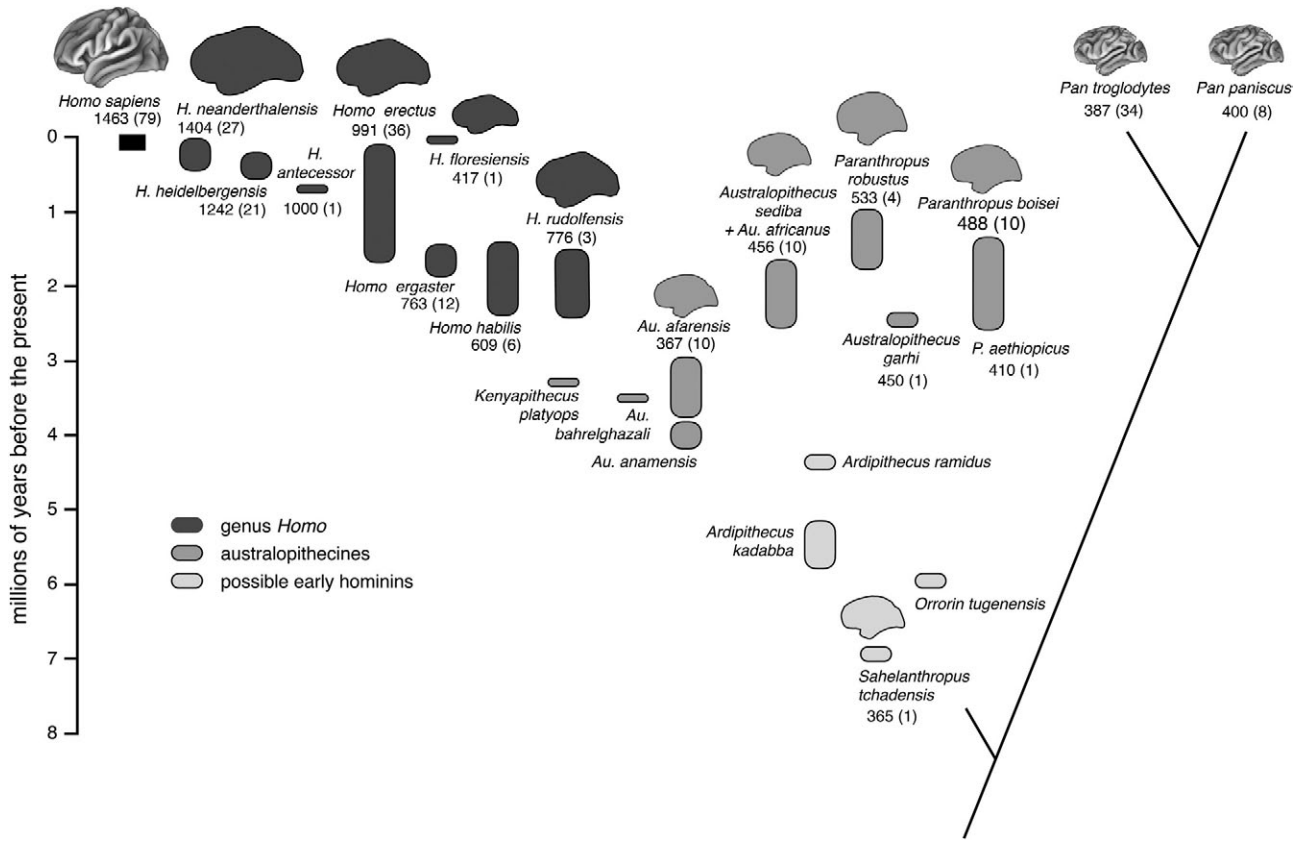

FIGURE 8.2 The fossil record of hominin phylogeny and brain size evolution. Date ranges for fossils are from Wood and Baker (2011). Brain sizes (in cubic centimeters) are from de Sousa and Cunha (2012) and, for *Pan paniscus* only, from Hopkins et al. (2009). Sample sizes are indicated in parentheses. Wood and Baker are not explicit about the details of relationships among each of the species, but there is general agreement that the genus *Homo* evolved from an australopithecine ancestor.

SOME BASIC NEUROANATOMY

It is not possible to give anything like a detailed account of human brain structure here; instead, I will introduce the structures most germane to the remainder of the chapter, mainly the cortex and related structures.

It is convenient to divide the brain into the cerebrum and the brainstem (Fig. 8.3). The paired cerebral hemispheres are covered by the gray matter of the cerebral cortex, a thin band composed of cell bodies (neurons and glia), nerve fibers, and blood vessels beneath which lies the white matter, composed mainly of the axons of nerve cells traveling between different cortical regions and between the cortex and structures deep in the hemispheres and in the brainstem. The cells of the cortex are stratified into six layers (Fig. 8.4A–C), each of which receives a specific set of incoming fibers and gives rise to a specific set of outgoing fibers. The cells of different layers are also interconnected, with the strongest local (intrinsic) connections being organized so as to link cells into vertical arrays, often termed "mini-columns." Mini-columns are considered to be fundamental units of the information-processing architecture of the cortex. Groups of adjacent cell arrays form larger units, termed "areas," which share common inputs, outputs, and intrinsic connections. Sometimes these areas can be distinguished by microscopic examination, because when stained for cells they have distinctively layering of cells or cells of unusual size or density or because of some other distinctive histological feature, such as horizontal and vertical distribution of myelinated fibers (Fig. 8.4D and E). These microscopic approaches are called "cytoarchitecture" (or cytoarchitectonics) and "myeloarchitecture," respectively. Even larger divisions are the lobes of the cerebral cortex, including the frontal, parietal, temporal, and occipital lobes, which are named for the skull bones that overlie them (Fig. 8.3).

Each lobe contains numerous areas, which fall into several types. There are the primary sensory areas, including the primary visual, auditory, and somatosensory areas (Fig. 8.5). They are termed "primary" because they receive strong and direct projections from divisions of the thalamus, a structure at the top of the brainstem that themselves receive strong inputs from the sensory systems,

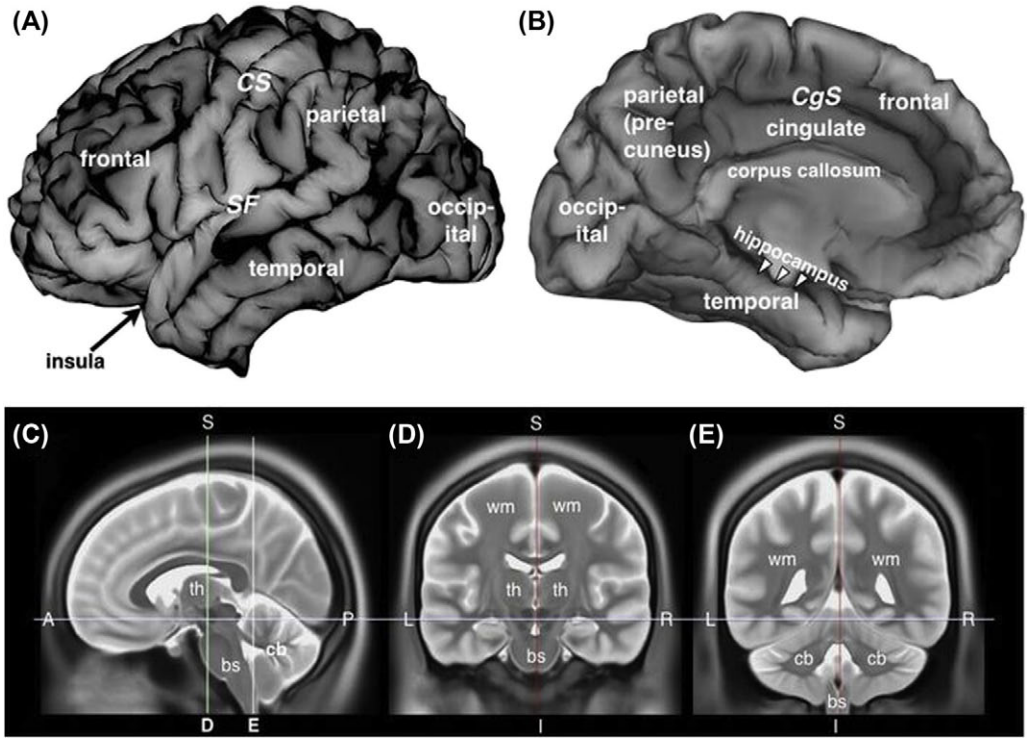

FIGURE 8.3 Human brain morphology. (A, B) The location of the major lobes are shown in lateral (A) and medial (B) views of the left cerebral hemisphere. The central sulcus (CS) separates the frontal and parietal lobes; the Sylvian fissure (SF) separates the temporal lobe from the frontal and parietal lobes. The insula is a region of limbic cortex buried within the SF. The cingulate sulcus (CgS) separates the cingulate cortex from the frontal and parietal cortex. (C–E) T2-weighted MRI images showing the relationship of the cerebral hemispheres to deep structures, including the thalamus (th), cerebellum (cb), and brainstem (bs). The section in C is in a parasagittal plane, with anterior (A) to the left. D and E are coronal sections; their locations are marked in C. In T2-weighted images, the cortical gray matter appears as a light rim surrounding the darker white matter (wm). Images were captured from the Human Connectome Project (HCP) datasets using HCP Workbench software (Van Essen et al., 2013). Additional abbreviations: *I*, inferior; *L*, left; *P*, posterior; *R*, right.

with the result that neurons in the primary areas respond rapidly to stimulation of their corresponding sense organs. There is also a primary motor area, which sends strong projections to the motor neurons of the spinal cord, and so gives rise to brisk movements when stimulated electrically. Whereas in most mammals, the primary areas occupy a large fraction of the total cortex, the cortical mantle of anthropoid primates is dominated by nonprimary cortex, which consists of secondary sensory areas and higher-order association cortex. In primates, each primary sensory area is connected with a set of secondary areas; these connections are organized partly in sequence (hierarchically) and partly in parallel, forming subnetworks that process different aspects of visual, auditory, and somatosensory information. Areas higher in the chain represent more complex features of stimuli. There is a similar arrangement for the motor system, with more complex or abstract facets of movement being represented in secondary areas, termed "premotor" areas in this system. For New World and Old World monkeys, these systems of areas and connections have been extensively studied over the past four decades (see, for example, the contributions in Kaas and Preuss, 2007).

The sensory and motor systems each occupy substantial portions of the lobes in which they reside—visual in the occipital lobe, auditory in the superior gyrus of the temporal lobe, somatosensory in the anterior parietal lobe, and motor in the posterior part of the frontal lobe. The rest of the cortex is conventionally referred to as the association cortex. We have known for over a century, based on observation of individuals with brain injuries, that the association cortex is critically involved in higher-order cognitive functions: Damage to temporal and parietal association cortices disrupts specific perceptual functions, while damage to the frontal association cortex (the so-called prefrontal cortex) and to portions of the parietal association cortex disrupts the organization of action and cognition on both short and long time scales. Like the sensory regions, the association cortex consists of collections of functionally specialized areas, as indicated by lesion studies and confirmed by neuroimaging. The idea that the association cortex functions as an undifferentiated

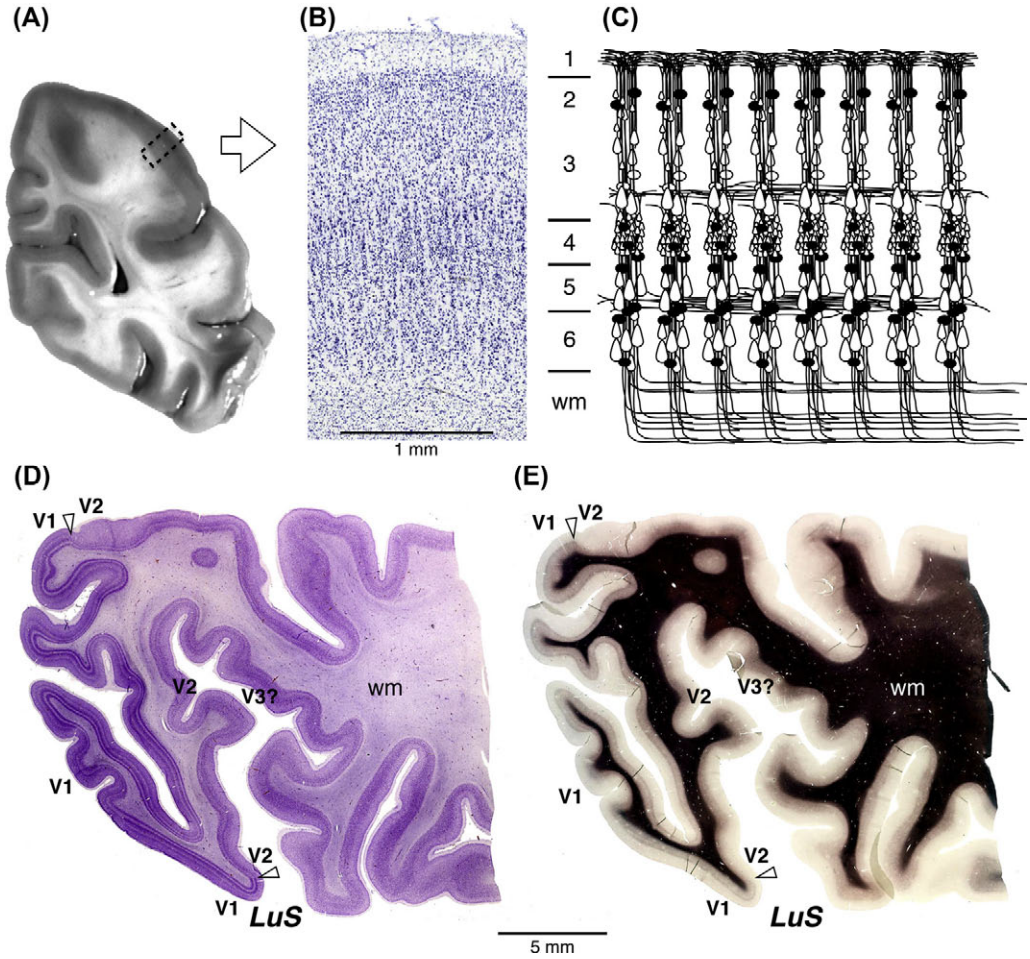

FIGURE 8.4 Laminar, columnar, and areal organization of cerebral cortex. (A) An unstained section through the posterior right cerebral hemisphere of a human; the inset shows the small region of gray matter illustrated at higher magnification in B. (B) A section of cortical gray matter stained for Nissl substance to illustrate the six tangential layers and the vertically oriented mini-columns. In this section, the columnar appearance of the cortex is most obvious in layers 4 and 5. (C) A schematic representation of cortical microstructure, showing the vertical clustering of neurons and the predominantly vertical, intracolumnar organization of intrinsic (local) connections, although some layers also have prominent horizontal, intralaminar connections as well. Most long connections travel in the white matter (wm). Collections of continuous minicolumns, with similar connections and cellular organization, make up the areas, the next higher-order unit. (D, E) Low-magnification view of a horizontal section through the posterior right hemisphere of an orangutan, stained for Nissl (D) and myelin (E) to illustrate cyto- and myeloarchitectonic differences between cortical areas. Posterior is to the left, lateral to the bottom. In both stains, the distinctive, highly laminated character of the primary visual area (V1) is apparent, and the border between V1 and the second visual area (V2), marked with arrowheads, is easily identified. Laterally, the border is close to the lip of the lunate sulcus (LuS, a deep fissure in apes and macaques, but absent in monkeys). While the other cortex in these sections is not homogeneous in Nissl or myelin, distinct borders, such as that between V2 and V3, which presumably occupies the anterior bank of the LuS, are often difficult to distinguish.

whole, as famously claimed by the influential neuropsychologist Karl Lashley (1949), cannot be sustained. That said, the association areas do not function in isolation, but rather participate in transcortical networks of interconnected areas that span multiple lobes and instantiate specific functions. These networks were first identified in macaque monkeys (see especially Goldman-Rakic, 1988), using chemical tracer techniques, and later in humans and nonhuman primates, using neuroimaging methods (eg, Li et al., 2013; van den Heuvel and Sporns, 2013; Yeo et al., 2011). It is important to note that the distinction between secondary sensory areas and the association cortex is somewhat arbitrary, especially in the parietal and temporal lobes, where areas involved in the identification of objects and actions are typically dominated by the analysis of visual features.

In addition to the sensory, motor, and association areas, the cortical mantle includes a number of "limbic" regions, located along the margins of the cortical mantle in the cingulate gyrus and the insular island, the latter buried deep in the lateral fissure. These regions link cortex (mainly the association cortex) with outposts of the autonomic nervous system in the brainstem that regulate emotion and motivation, and with the hippocampus, a specialized region at

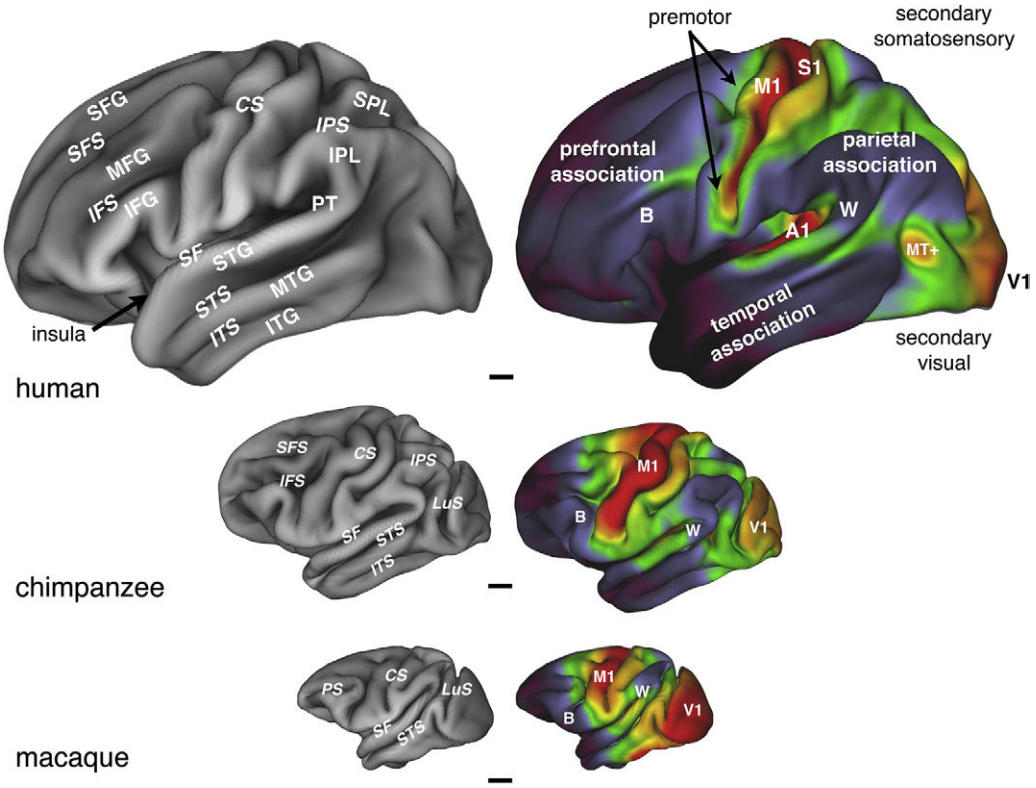

FIGURE 8.5 The major sulci, gyri, and functional divisions of the cortex in humans, chimpanzees, and macaques. These are lateral views of the left cerebral hemisphere drawn to scale. Figurines in the left panel illustrate similarities and differences in the folding patterns of the three species. Both chimpanzees and macaques possess a deep lunate sulcus (LuS), which separates primary visual cortex (V1) from secondary visual areas; humans lack an LuS. Also, macaque frontal lobes have a single longitudinal fissure, the principal sulcus (PS) rather than the two longitudinal fissures present in chimpanzees and humans, the inferior and superior frontal sulci (IFS, SFS). Figurines in the right panel display color maps of the myelin density across the cortex. The densely myelinated primary sensory areas—visual (V1), somatosensory (S1), and auditory (A1) are red, as is the primary motor area (M1). The densely myelinated middle temporal visual region (MT+) is largely exposed on the surface in humans, but buried within the posterior part of STS in chimpanzees and macaques. The secondary sensory and premotor areas, somewhat less heavily myelinated, shade from red to green. The higher-order association regions are mainly blue. Association cortex makes up a much greater fraction of the cortical mantle in humans than in chimpanzees or macaques. Additional abbreviations: *B*, Broca's area; *CS*, central sulcus; *IFG*, inferior frontal gyrus; *IP*, inferior parietal lobule; *IPS*, intraparietal sulcus; *ITG*, inferior temporal gyrus; *ITS*, inferior temporal sulcus; *MFG*, middle frontal gyrus; *MTG*, middle temporal gyrus; *MT+*, the middle temporal visual complex; *PT*, *planum temporale*; *SF*, Sylvian fissure; *SFG*, superior frontal gyrus; *SPL*, superior parietal lobule; *STG*, superior temporal gyrus; *STS*, superior temporal sulcus; *W*, Wernicke's area. *Images were captured from the Human Connectome Project (HCP) datasets using HCP Workbench software; the chimpanzee and macaque data are from scans collected at the Yerkes National Primate Research Center, processed through HCP pipelines. Scale bar is 1 cm.*

the extreme margin of the cortical mantle involved in memory.

The left and right hemispheres of the human brain are notably asymmetric in several features. For example, the human brain exhibits torque, the right frontal lobe extended further anteriorly than the left, and the left occipital lobe further posteriorly than the right. Also, the folding patterns in Broca's region differ on the left and right, as do the patterns in the posterior language region, where the Sylvian fissure extends into the parietotemporal junction region. The differences in the latter region are attributable at least in part to the larger size, on average, of the *planum temporale* in the left hemisphere, that is, the cortical territory immediately posterior to primary auditory cortex that is usually identified with Wernicke's area proper (Geschwind and Levitsky, 1968).

THEMES AND THEORIES IN HUMAN BRAIN EVOLUTION

Before considering current evidence about human brain evolution, it is useful to review some of the ideas that emerged prior to the advent of techniques that allow us to directly compare the internal organization of human and nonhuman primate brains, as these ideas remain influential.

Association Cortex Enlargement by the Addition of Areas

It is commonly thought that the evolutionary enlargement of the human brain resulted from expansion of the association cortex. An important proponent of this view was Korbinian Brodmann (1909), whose comparative cortical

maps remain staples of neuroscience textbooks today. Brodmann charted cortical areas in humans based on differences in cytoarchitecture; in the same era, others produced maps based on myeloarchitecture. Brodmann's results seemed to indicate that species with larger cortices have more discrete cortical areas. In humans, for example, Brodmann recognized divisions within Broca's area (areas 44 and 45) and in the association cortex of the inferior parietal lobule (IPL; areas 40 and 39) that he did not recognize in other primates. He also argued for the expansion of the prefrontal cortex in human evolution (Brodmann, 1912). Much later, using more reliable anatomic and physiological mapping techniques than those available to Brodmann, John Allman and Jon Kaas summarized evidence indicating that larger-brained mammals generally have more cortical areas than smaller-brained species (Allman, 1982; Kaas, 1987), although they did not have data for apes or humans. The idea that enlargement of the human brain proceeded by the addition of new areas is thus reasonable, and its appeal is probably enhanced by the intuition that human-specific cognitive functions, such as language, are likely to be instantiated by human-unique brain areas (eg, Crick and Jones, 1993; Geschwind, 1970).

Association Cortex Expansion, Without Internal Compartmentation

While enlargement of the association cortex was widely accepted throughout the 20th century, its organization was hotly disputed. Most scientists accepted that the association cortex contained multiple subdivisions, with different functions, but there was little agreement about the exact number of areas or the location of the borders between them. Lashley (1949) concluded there really were no divisions, that the association cortex operated as an undifferentiated whole, and that what mattered functionally was the amount of cortex possessed by different species.

If this is the case, then brain size is a highly meaningful variable. There is a complication, however, brain size varies with body size, but they do not vary proportionally (isometrically): as body size increases, so does brain size, but not to the same extent. In order to compare the relative brain sizes of species that differ in body size, one must take this allometric relationship into account. The classical approach to this is to take brain and body sizes for a large sample of mammals, log transform the data (which turns the plot into something more nearly linear), and then fit a line using regression. The result is a baseline for assessing relative brain size, an equation for generating the expected value of brain size for a mammal of a given body size. This was the approach taken by Harry Jerison (1973) in his classic work. Although Jerison was not the first to do this, his underlying theoretical approach was an expression of Lashley's ideas, in which the brain is composed of two compartments, one that scales with brain size, and another—the association cortex, essentially—that does not. In addition, he provided a way to express relative brain size with his encephalization quotient (EQ), which is simply the ratio of the observed brain size for a species divided by the brain size expected for a mammal of that brain size. Significantly, Jerison believed EQ could be understood as an index of behavioral or cognitive capacity: "biological intelligence," in his argot. In his original formulation, he took no account of possible species differences in the organization of the cortex, apart from size, and he followed Lashley in assuming association cortex is internally undifferentiated (although he subsequently acknowledged such differentiation; Jerison, 1977). According to Jerison, human brains are about 7–8 times the size of an average mammal.

Association Cortex Enlargement With the Same Areas, but Reorganized

Despite the influence of Lashley on brain-evolutionary studies—mainly through Jerison's work—his core idea that the association cortex is structurally and functionally undifferentiated did not win wide favor. Nevertheless, by the mid-20th century, the large number of areas proposed by Brodmann was seen as excessive. The view emerged that although the association cortex was not homogeneous, the number of constituent areas was relatively small and did not increase in human evolution (Bailey and Bonin, 1951; Bailey et al., 1950; Bonin and Bailey, 1947, 1961). More recently, Petrifies and Panda (1994) remapped the cytoarchitecture of frontal cortex in humans and macaques, and concluded that both species possess the same complement of areas.

If there are, in fact, no new areas in human cortex, what changes took place that could account for the evolution of human cognitive specializations? In a seminal paper, Holloway (Holloway, 1966; see also Holloway, 2008), under the general rubric of "reorganization," considered a variety of other types of change, including a general expansion of existing areas, changes in the relative sizes of different structures, changes in the way structures are interconnected, hemispheric differences, and changes in brain microstructure, such as in the density and distribution of specific receptor molecules across cortical areas. Although Holloway is best known for his later research on brain endocasts of extinct and extant species, his conceptualization of possible changes in brain internal organization, articulated in the 1960s when little was known in detail about cortical organization, was remarkable. It served as an inspiration to new generations of scientists (including this author), when techniques became available for comparing the internal

brain organization of living species (Broadfield and Holloway, 2010).

Humans as Scaled-Up Apes

The modern appreciation of just how closely humans are related to the African great apes has exerted a significant influence on how scientists have viewed human brain evolution and the molecular mechanisms involved. In their classic paper, King and Wilson (1975) noted that, for the proteins and protein-coding genes studied up to that time, humans and chimpanzees were identical on average at 98–99% of nucleotide or amino-acid positions: remarkably similar, given the apparent behavioral and other phenotypic differences between humans and apes. To explain the disparity, they proposed that the phenotypic differences resulted from changes in genes that regulate the expression of other genes, which could result in a common set of genes and proteins being expressed in different quantities and at different points in development in different species. Picking up on this idea, Gould (1977) argued that changes in regulatory genes would have especially profound phenotypic effects if they acted early in development, and a human-like phenotype, with a large brain and small face, could be produced from a chimpanzee-like ancestor by extending early developmental programs and truncating later ones, a phenomenon known as neoteny.

This kind of thinking invites consideration of how species differences might be understood as predictable outcomes of general rules of development. Finlay and Darlington (1995) noted that the sequence in which different parts of the brain region emerge in development is widely conserved across mammals, with cells in brainstem structures generated early and cells in the forebrain generated later, with cortical cells latest of all. Large-brained mammals, however, develop over a longer timespan than small-brained mammals, and the effect of extending development is not linear—later developing structures show disproportionately protracted periods of cell generation, and thus are disproportionately enlarged in adults. Because of the evident tight coupling of brain structures in development, one can predict the sizes of brain structures from total brain size (except for olfactory structures, which play by a different set of rules).

From this perspective, it is a small step to viewing the human brain as a scaled-up version of an ape brain—a simple extension of the ape plan—at least with respect to size. Semendeferi and colleagues examined the proportions of the frontal, parietal, and temporal lobes in humans and apes, and found that although these lobes are larger in humans, they occupy about the same fraction of total cortex in all these species (Semendeferi and Damasio, 2000; Semendeferi et al., 2002). On this basis, they disputed the claim that the prefrontal association cortex was differentially expanded in human evolution, although they did not measure prefrontal cortex directly (which is difficult to do without histological examination of tissue). The same inference would follow for the parietal and temporal association regions. Others have made the same point, noting that in regression analyses, the amount of frontal cortex (or temporal cortex, or cortex generally) in humans is about what would be expected for a great ape of our brain size—larger, absolutely, but not disproportionately large (Barton and Venditti, 2013; Bush and Allman, 2004; Holloway, 2002; Passingham, 1973; Rilling and Insel, 1999). These findings have prompted the suggestion that any cognitive differences in humans involving the frontal lobe are not related to its overall relative size, but rather to changes in the proportions of different areas, and in their microstructure and connectivity (Semendeferi et al., 2002; Teffer and Semendeferi, 2012).

EVOLUTION OF BRAIN SIZE AND EXTERNAL MORPHOLOGY

Brain size is an attractive variable for scientists, having the virtue of being measurable in both living and extinct species. For this reason, and because cortical organization and its variations across mammalian groups were very poorly understood for much of the 20th century, studies of brain evolution during that period strongly emphasized the evolution of relative brain size (encephalization). Jerison's (1973) methodology was highly influential, although not without challenge. The correct assessment of relative brain size (EQ) depends on the slope of the regression line used to generate expected brain size for a given body weight: higher slopes will yield smaller EQs for larger-bodied species and higher EQs for smaller-bodied species. Jerison favored a slope of 2/3, whereas Martin (1981) argued for 3/4, based on a larger sample of species. Today, however, perhaps because of growing appreciation of the diversity of brain structure among mammals as well as of the variations in body proportions and composition, it is not obvious that there is or should be a single baseline for all mammals.

One consequence of the diversity of brain organization is that it compromises the utility of EQ as an index of cognitive capacity: species with similar EQs can have brains organized quite differently (Holloway, 1966). Nevertheless, comparisons of relative brain size among closely related species remain useful, because marked changes in size suggest the action of selection to modify cortical functions and cognitive capacities. The matter is rendered simpler if the species in question are similar in body size, in which case the distinction between absolute and relative brain size dissolves. To a first approximation, this is the case with humans and the other members of the great ape clade. Average adult human body size falls between that of

chimpanzees and gorillas (de Sousa and Wood, 2007; Leigh and Shea, 1996). Human brains average about 1450 cm^3 in volume, however, whereas chimpanzee and gorilla brains average about 380–400 cm^3 (Barks et al., 2015a; de Sousa and Wood, 2007; Schoenemann, 2006), so humans are about 3–4 times as encephalized as our African ape relatives. For comparison, rhesus macaque brains average about 90 cm^3 (Herndon et al., 1998), so human brains are about 14 times as large, but macaques also have much smaller bodies than apes or humans. One recent allometric analysis suggests there are three different levels (or grades) of encephalization among Old World anthropoid primates, with macaques and other Old World monkeys, plus gibbons, constituting one level, the great apes a higher level, and humans a higher level still (Passingham and Smaers, 2014).

These comparisons suggest that humans underwent enormous brain enlargement since the divergence of the human lineage from those leading to the other African hominoids, ~5–8 Ma (dates reviewed by Langergraber et al., 2012), even allowing for the possibility that chimpanzees and gorillas underwent some independent brain enlargement (Fig. 8.2). Even early hominins, such as *Australopithecus* and *Paranthropus*, appear to have been modestly encephalized compared to the living African apes, having smaller bodies but slightly larger brains (de Sousa and Wood, 2007), with a trend toward increasing encephalization through time. One long-running controversy concerns the location in australopithecines of the lunate sulcus, which in apes and most monkeys separates the primary visual cortex, located at the posterior pole of the hemisphere, from the remainder of the cortex (Figs. 8.4 and 8.5) (for reviews, see Falk, 2014; Holloway, 2008). Early accounts of the first australopithecine fossil discovered in 1924 at Taung in South Africa, which includes a partial natural brain endocast, argued that the lunate was displaced posteriorly compared to apes, suggesting an expansion of the association cortex. Falk (1980) later argued that the Taung lunate is actually located in a more anterior, ape-like location. Holloway (1981) responded that the lunate was not preserved on the Taung endocast, but other features suggested association cortex enlargement. My view is that the sulcal patterns of Taung and other australopithecines are quite chimpanzee-like; at the same time, the likelihood that australopithecines are slightly encephalized compared to living apes makes some degree of association cortex expansion plausible as well.

A dramatic acceleration of brain volume began with the appearance of the genus *Homo*, however, by about 2.5 Ma, close in time to the appearance of the oldest stone tools, assigned to the Oldowan tradition, followed several hundred thousand years later by the more complex tools of the Acheulean tradition (Stout, 2011). Nearly modern brain size was achieved perhaps as early as 500,000 years ago, with *Homo heidelbergensis*; a later hominin, *Homo neanderthalensis*, which evolved largely independently of our own species, had a brain of nearly equivalent average size (reviewed in de Sousa and Wood, 2007; Holloway et al., 2009). However, *Homo sapiens* has a distinctive brain shape, sometimes characterized as globular, contrasting with the more elongated form of other members of the genus *Homo* (Bruner, 2004). This may be related to an expansion of the medial part of posterior parietal cortex, the precuneus (Bruner et al., 2016). This shape change occurred at a time when indicators of modern human behavior, such as decorative objects, items of personal adornment, fine blades, increasingly standardized tool types, and long-distance material exchange, first appeared in the archeological record, beginning by around 200,000 years ago, in Africa (Mcbrearty and Brooks, 2000).

Evolutionary increases in total brain size reflect mainly changes in the cortical gray matter and associated white matter, which make up the largest fraction of brain volume. There likely were size changes in other structures as well, but because the cortex is connected with many other structures—both physically, in adults, by means of axonal connections, but also in development, as described above—it is difficult to identify changes that occurred independently. For example, humans have larger cerebella than do chimpanzees or monkeys, and the prefrontal cortex projection to the cerebellum is much larger in humans than in other primates (Balsters et al., 2010). Did the cerebellum enlarge as a consequence of prefrontal expansion, or vice versa?

The prominent left-right asymmetries of the cerebral hemispheres are commonly viewed as the basis of the distinctive behavioral lateralities of humans, principally our overwhelming right-handedness (at a population level) and left-hemisphere dominance for language. Nevertheless, apes show many of the same asymmetries of gross brain morphology as humans, at least qualitatively (Cantalupo et al., 2009; Gannon et al., 1998; Gilissen and Hopkins, 2013; Holloway and de la Coste-Lareymondie, 1982; Hopkins and Marino, 2000; Hopkins and Nir, 2010). For this reason, it has been argued that the anatomical foundations of human communication, gesture, and manipulation were inherited from our hominoid ancestors (Cantalupo et al., 2009). So, it is currently unclear whether there are human-unique asymmetries, at least at the level of external morphology. This remains an area of active investigation, however, and it has been claimed that humans, but not chimpanzees, have a strong asymmetry within a region of higher-order association cortex, the middle portion of the human superior temporal sulcus (Leroy et al., 2015). Moreover, as discussed below, there is evidence for human specializations of hemispheric asymmetry at finer levels of brain organization.

INTERNAL CHANGES

Enlargement of Higher-Order Cortex and Thalamus

There are few conclusions one can state with great confidence about human brain evolution, but one can confidently assert that humans have a much larger proportion of the cortical mantle devoted to the higher-order, nonprimary cortex (the association cortex and secondary sensory regions) than do apes or monkeys. Evidence from both classical and modern work unambiguously supports the idea that the primary cortical areas are about the same size in human and apes and that nonprimary regions are much larger. The quantitative work of Brodmann (1912), Blinkov and Glezer (1968), Deacon (1997), and Passingham (1998), reinforces the impression of differential enlargement obtained from simple visual inspection of the architectonic maps of humans and nonhuman primates. Cell counts in the thalamic nuclei that project to the different parts of the cortex tell much the same story, the primary sensory nuclei having about the same numbers of neurons in humans and great apes, while the association nuclei have several-fold more in humans (Armstrong, 1982).

Recent analyses, using data from comparative MRI research, also support this conclusion. Avants et al. (2006) compared humans and chimpanzees, using an approach that involves identifying homologous landmarks in the cortex and then "deforming" one species to match the other, concluded that frontal and temporal association cortex are about twice as large in humans, relative to total cortical volume. Another approach involves using MRI to measure and map the myelin content of gray matter (Glasser and Van Essen, 2011), which is useful because primary and secondary areas tend to be heavily myelinated, while association areas tend to be lightly myelinated. When applied to humans, chimpanzees, and macaques with comparable imaging protocols, the much greater extent of association cortex in humans, in both relative and absolute terms, is dramatically apparent (Glasser et al., 2014) (Fig. 8.5).

How do we reconcile these results with the finding that the major lobes of the brain are about the same proportions in humans and apes? The major lobes contain a mixture of primary, secondary, and association cortex; if the primary areas are relatively static in size in human evolution, we need to only assume that the nonprimary cortex expanded to similar extents in the different lobes. This is reasonable, given the strong connections and functional dependencies between association regions (eg, Goldman-Rakic, 1988; Yeo et al., 2011). These dependencies are highlighted by the discovery that the association cortex is the home of a number of connectivity "hubs," that is, key nodes in networks that link areas dispersed among the different lobes (eg, Buckner et al., 2009; Li et al., 2013; van den Heuvel and Sporns, 2013). A similar argument has been advanced by Barton and Venditii (2013).

What about the claim that humans have about as much frontal cortex—or prefrontal cortex, or association cortex—as would be expected for a great ape of our brain size? The validity of this claim, with respect to prefrontal cortex specifically, has been disputed (Deacon, 1997; Passingham and Smaers, 2014), but for the sake of argument, let us assume it is true. Does it matter? One would never expect a nonhuman primate to have a brain of our size: apes of our body size have brains of about 400 cm^3 in size, rather than 1400−1500 cm^3, and the difference is almost entirely due to the greater amount of secondary and higher-order association cortex (and underlying white matter) in humans. There is simply no getting around the fact that humans have a lot more neural machinery devoted to higher-order systems than do other primates, and while this is not the only difference in brain organization between humans and apes, it must be an important one. The question of whether the amount of association cortex humans possess is similar to that predicted for a primate of our brain size might bear on the question of how humans came to have such capacious association regions—perhaps it is the case that humans follow a primate-general law of growth (Finlay and Darlington, 1995)—but that doesn't make those regions any less enormous (Passingham, 2002; Preuss, 2011).

Changes in Areal Organization, Function, and Connectivity

Turning to matters of how evolution modified the internal structure, connectivity, and function of cortex, it is useful to start with a detailed analysis of language. This is because we know a great deal about its neural substrates in humans, because there are numerous studies bearing on whether homologous structures and systems exist in nonhuman primates, and because language has been a central focus in discussions of human brain evolution and human psychological uniqueness. As it happens, the language system exemplifies the variety of modifications that occurred during human brain evolution.

It is reasonable to suppose that the evolution of language, as one of the key specializations of humans comprising a set of functions that engages a remarkably large fraction of the cortex (Price, 2012), has had a huge impact on human brain organization. Not surprisingly, the classical frontal and temporoparietal language regions—Broca's and Wernicke's areas—have sometimes been treated, explicitly or implicitly, as uniquely human (eg, Brodmann, 1909; Crick and Jones, 1993; Geschwind, 1970). Nevertheless, there is a clear consensus among those

who have studied the issue that there are homologues of Broca's and Wernicke's areas in chimpanzees, macaques, and other nonhuman primates, based on similarities in cytoarchitecture, location relative to other cortical areas, and nonlinguistic functional and physiological characteristics, such as representation of species-specific calls (for reviews, see Aboitiz, 2012; Arbib, 2012; Deacon, 2006; Ghazanfar and Miller, 2006; Preuss, 2011; Rilling and Stout, 2014; Schoenemann, 2012; Sherwood et al., 2008). In fact, the idea that a homologue of Broca's area, at least, is present in nonhuman primates dates back at least as far as Bonin (1944), who suggested that this area was "recruited" to language in human evolution (as discussed in Preuss, 1995).

If evolution "recruited" Broca's and Wernicke's area to support language, it must have modified them in some ways. Currently, there is evidence for major changes in the long-distance, extrinsic connections of language cortex. In humans, fibers connecting the frontal and posterior language regions were classically thought to travel in a distinct fiber bundle, the arcuate fasciculus (Geschwind, 1970). Because the trajectories of fibers through the white matter can be tracked with DWI, the organization and distribution of arcuate fibers was the first connectivity system to be studied using comparative DWI in humans, chimpanzees, and macaques (Rilling et al., 2008, 2011). Rilling and colleagues found two pathways interconnecting the inferior frontal gyrus (Broca's area) and posterior superior temporal gyrus (STG), including its most posterior segment, the *planum temporale* (Wernicke's area, as often construed). These include a dorsal pathway running deep to the lateral parietal and frontal cortex, corresponding to the arcuate fasciculus, and a ventral pathway, running deep to the insula. Interestingly, the dorsal pathway is larger on the left than the right in both humans and chimpanzees, as is the size of the *planum temporale* (Gannon et al., 1998). The arcuate pathway is enlarged relative to the ventral pathway in humans compared to chimpanzees; moreover, in humans, but not in chimpanzees or macaques, the main termini of arcuate fibers in the temporal lobe is actually inferior to the *planum temporale*, in the posterior STG and middle temporal gyrus (MTG). In humans, this MTG region, which is located immediately anterior to a region of higher-order visual representation (the area MT + complex), is known to be involved in representation of word meanings, and in semantic representation more generally. It is also connected with areas in posterior parietal cortex involved in tool use (Ramayya et al., 2010).

These results raise the question whether changes in human arcuate anatomy represent only changes in connectivity, or whether the MTG semantic region is an area lacking in nonhuman primates. Currently, there is no evidence for an MTG semantic-area homologue in nonhuman primates; if there is, it must have been highly modified in hominoid or hominin evolution. Similar issues arise when we consider the extended language system. For example, in humans, cortex at the anterior pole of the temporal lobe is also thought to be involved in semantic representation (Jefferies, 2013), and there is currently no plausible homologue known in macaques (much less in chimpanzees).

Presumably, changes in the functions of areas involved in language were accompanied by changes in the internal, microstructural organization of areas. In fact, the spatial organization of neurons in Broca's and Wernicke's areas is different in humans compared to chimpanzees and macaques. Specifically, the spacing between the vertical neuronal arrays (minicolumns) of Broca's and Wernicke's areas is greater in the left hemisphere than the right in humans, but not in the nonhumans (Buxhoeveden et al., 2001; Schenker et al., 2008). While these results have been interpreted as indicating increased space for synaptic processing in the left, language-dominant hemisphere, we currently know nothing about specific patterns of connections between neurons in these areas and how they differ across species.

From the language system, then, we have evidence for evolutionary modifications in the functions of preexisting areas, changes in extrinsic cortico-cortical connectivity, and changes in microstructure. While it is possible that the complement of cortical areas is not identical in humans, chimpanzees, and macaques, we lack clear evidence of human-unique areas.

Next to language, probably the best studied system, from a comparative perspective, is the distributed network of frontal, posterior parietal, and temporal areas involved in the visually guided control of object grasping and manipulation. This is sometimes referred to as the mirror system, because similar patterns of cortical activation result when an experimental participant observes another individual grasping an object with the hands or mouth, or when the participant makes that movement themselves (Buccino et al., 2001). There is good reason to think this system was modified in evolution. For one, the system includes areas that are engaged when humans manipulate or make tools, including stone tools, as demonstrated in experimental studies of human subjects taught to make Oldowan and Acheulean implements (Stout et al., 2011). For another, there are important species differences in imitative proclivities (Whiten et al., 2009): Humans are extreme imitators, focusing on the forms and sequences of action, even when some of the elements of the action are not necessary to produce the intended outcome. Macaques, by contrast, have very limited abilities to copy actions. Chimpanzees can copy actions but are less inclined than humans to copy actions that have no functional consequences. In humans, furthermore, areas of the mirror system are activated when actions are directed toward an object (transitive movements) or when they are merely mimed (intransitive

movements); in macaques, they are activated only when viewing transitive movements (Buccino et al., 2001).

Hecht et al. (2013) carried out comparative neuroimaging studies of the mirror system. Using positron-emission tomography (PET), a functional imaging technique, they compared cortical activity in humans and chimpanzees while subjects grasped an object, or observed others grasping the same object (transitive condition), or observed another miming the action (intransitive condition). In one respect, chimpanzees were similar to humans, showing increased activation in the intransitive condition, as well as in the transitive observation and grasping conditions. Both species, furthermore, showed activation in frontal and parietal cortex, although chimpanzees showed relatively greater activation of frontal than parietal cortex compared to humans. In addition, humans showed considerable activation in the temporal lobe, including the posterior MTG, whereas there was little temporal-lobe activation in chimpanzees. The authors suggest that the bias toward frontal activation in chimpanzees is consistent with their greater propensity for copying outcomes than the details of action, the latter involving representations in posterior cortex. Interestingly, macaques are reported to show greater activation of frontal cortex relative to secondary visual cortex than humans while viewing objects (Denys et al., 2004).

Subsequent examination of the connections between cortical elements of the mirror system in humans, chimpanzees, and macaques, using DWI, found that all three species have connections between the inferior frontal gyrus, the IPL, and portions of temporal cortex (Hecht et al., 2015a). Compared to macaques, however, chimpanzees and humans showed greater connectivity between the temporal and parietal cortex, while humans showed even further enhancement of temporal connectivity with the parietal cortex, including connections with portions of the superior parietal cortex related to spatial attention, as well as stronger parietofrontal connections overall than chimpanzees or macaques. Evidently, the connections of the mirror system were modified in hominoid and human evolution, with the possible recruitment of additional cortical areas into the network in humans. Whether those areas have homologues in nonhuman primates remains to be determined.

Hecht and colleagues have also compared the sizes and distributions of the major fiber bundles that interconnect the frontal and parietal lobes—that is, the different divisions of the superior longitudinal fasciculus (SLF)—in humans and chimpanzees (Hecht et al., 2015a). They report that the inferior limb of SLF (SLFIII), which connects cortical regions involved in the higher-order control of grasping and manipulation—the anterior inferior parietal cortex and ventral premotor and prefrontal cortex—makes up a significantly larger fraction of total SLF volume in humans than in chimpanzees. In addition, SLFIII is right-lateralized in humans, but not chimpanzees. In humans, the right inferior frontal gyrus is thought to be specialized for fine motor control (Liakakis et al., 2011), and in experimental studies of stone-tool making, the right inferior parietal and ventral frontal cortex are activated more when individuals make Acheulean tools compared to the simpler Oldowan tools (Stout et al., 2011). Moreover, training individuals to make tools results in structural enhancement of the SLFIII and increased volume of the frontal and parietal areas it connects (Hecht et al., 2015b). These results suggest that right inferior parietofrontal networks were modified in human evolution.

A third system that has been studied in humans, chimpanzees, and macaques is the so-called default-mode network (DMN). The DMN was discovered in human neuroimaging experiments as a set of areas that are activated when subjects rest in the scanner, not engaged in any externally driven task, but are deactivated when such tasks are initiated: hence the characterization as "default" (Buckner, 2012; Raichle et al., 2001). Subjects report that while resting in the scanner, they daydream about past events in their lives, or about future plans, or about possible interactions with other persons (Buckner and Carroll, 2007). As it happens, there are experimental conditions that can activate the DMN, specifically conditions that cause subjects to think about social situations or to engage in self-examination; thus, the DMN and its constituent areas are now seen as components of the social brain and substrates of self-representation (Mars et al., 2012). There is evidence for important differences between humans and other primates in the realm of social cognition, including our unusual imitative proclivities, our sensitivity to rank and social status in evaluating truth claims and for modeling behavior (Henrich, 2015), and our sophisticated abilities to represent mental states and understand their operation (Povinelli and Eddy, 1996). Given this, one might expect there to be major human specializations of social cognitive systems, including the DMN. Nevertheless, there is good functional imaging evidence that the DMN exists in chimpanzees (Barks et al., 2015b; Rilling et al., 2007) and macaques (Mantini et al., 2011; Vincent et al., 2007), and includes many of the same anatomical areas as in humans, although it is not clear whether an identical set of areas and connections is involved in all three species.

The discussion above prioritized studies that included human-chimpanzee comparisons, these being necessary (if not sufficient) for identifying human specializations. It is useful, however, to also consider some of the recent neuroimaging studies comparing humans and macaques, because these make it clear that there was much evolutionary change in the functions of homologous areas in primate evolution, even if it is not always clear whether the

changes constitute human specializations, hominoid specializations, or macaque (or Old World monkey) specializations.

The posterior parietal cortex is of special interest because, in both humans and macaques, parietal-lobe lesions impair the ability to grasp and manipulate objects, and in both species, multiple areas along the intraparietal sulcus (IPS) and anterior IPL respond to the visual presentation of objects. Human and macaque parietal areas are sensitive to different qualities of motion, however. For example, Peeters et al. (2009) found that humans displayed enhanced responsiveness in the anterior IPL when shown video clips of an object being grasped by a tool compared to by a hand; macaques responded no differently to tools versus hands (Peeters et al., 2009, 2013). While the original study suggested the area in question might be uniquely human, the later study concluded that it is probably homologous to a division of macaque anterior IPL.

Vanduffel et al. (2002) showed subjects stick figures moving in two dimensions (ie, in a plane) or appearing to move in depth, including movement around an internal axis, giving the impression of a three-dimensional object (a structure-from-motion display). Both conditions activated lower-order visual areas and IPS cortex in both species, but humans showed greater activation of IPS cortex with the 3D structure-from-motion display than with the 2D display. At least some of the areas that show differential activation in humans probably have homologues in macaques, as the anatomical organization of this region is generally similar in humans and macaques (Mars et al., 2011).

Mantini and colleagues used functional MRI to extract networks of physiologically coupled areas (resting-state networks) in humans and macaques to identify potentially homologous networks, and to detect differences (Mantini et al., 2013). Most of the networks they identified have plausible homologues in both species, although the set of areas that make up a given network differs in some cases between humans and macaques. They did identify separate left and right frontoparietal networks in humans as being without counterparts in macaques; however, this might reflect a species difference in cortical lateralization, as the areas in question probably have homologues in both species and could belong to the ventral parietofrontal networks discussed above in relation to object manipulation.

Evidence for New Areas?

The evidence reviewed above strongly suggests that much of the action in brain evolution involved the modification of the connections and functions of areas common to humans and nonhuman primates. There is also some evidence that new areas evolved in the lineages under consideration. A survey of the functional connectivity of human and macaque temporal cortex identified a territory at the anterior end of the superior temporal sulcus (STS) lacking a definite counterpart in macaques, and having properties suggesting involvement in social cognition (Mars et al., 2013), which is consistent with results from task-based functional neuroimaging studies of humans (Zahn et al., 2007). Functional connectivity data also suggest that humans possess a region of frontopolar cortex (the lateral part of Brodmann's area 10) that is not present in macaques (Sallet et al., 2013). Area 10 is reportedly enlarged in humans compared to other apes and to monkeys (Semendeferi et al., 2001), raising the possibility that this is a human specialization. Probably the clearest evidence for differences in areal organization comes from studies of face-sensitive areas in the temporal lobe. Macaques have face-selective foci in the STS, while humans possess STS foci as well as one or more additional foci in the fusiform gyrus, comprising the so-called fusiform face area (Pinsk et al., 2008). While this likely represents a real difference in areal organization, there is reason to think it is not a human specialization, because a PET study in chimpanzees yielded face sensitive foci in both STS and fusiform gyrus (Parr et al., 2009), consistent with behavioral experiments indicating chimpanzees process faces in ways more similar to humans than to macaques (Parr, 2011).

To summarize, while there is evidence that new areas evolved in Old World anthropoid primates, it is currently unclear that there are new *human*, as opposed to hominoid, areas. Definitive resolution of this matter awaits the construction of cortical maps for chimpanzees comparable in resolution to those available for macaques and humans. Yet for one region, the frontal cortex, which is the part of the cortex that has been most carefully studied with respect to areal compartmentation and homologies, it is remarkable how little difference there is between humans and macaques: if not quite identical in areal organization (Petrides and Pandya, 1994), they nonetheless appear to be extremely similar (Neubert et al., 2014; Sallet et al., 2013).

Evolutionary Modifications of Sensory and Limbic Cortex

Given the traditional emphasis on modifications of association cortex in human evolution, one might suppose that other regions of the brain, such as sensory and limbic structures, were evolutionarily static. This is not the case. Although there have been few comparative studies of most of the sensory and motor regions, the visual cortex of humans and macaques has been intensively studied, and their organization compared (for a review, see Preuss, 2004). Both species possess, in addition to the primary visual area (V1, also known as "striate" cortex, because it has a prominent band of myelinated fibers in its middle layers; see Fig. 8.3), a large set of secondary, "extrastriate"

areas. Many of these are present in both species, and indeed, there are many areas common to both New World and Old World anthropoids (Lyon, 2007; Rosa and Tweedale, 2005). Collectively, the secondary visual areas appear to be larger, relative to the size of area V1, in humans (Van Essen et al., 2001; Vanduffel et al., 2014). Also, in the lateral occipital cortex, which is dominated by representation of central vision, recent human parcellations posit several cortical divisions (designated with the prefix LO) in addition to area V4 (Kolster et al., 2014), an area present in all primates that have been studied. There are also well-documented differences in the motion sensitivity of homologous cortical areas in the dorsal extrastriate cortex (Tootell et al., 1997; Vanduffel et al., 2001). Differences in these areas could contribute to the differences in parietal cortex motion sensitivities discussed above, although as with the parietal areas, without detailed studies of great apes, we cannot reconstruct the history of evolutionary change in extrastriate cortex.

In addition to sensory, motor, and association cortex, there are large territories along the margins of the cortical mantle—in the orbitofrontal and insular regions, laterally, and on the cingulate gyrus, medially—that are considered to be cortical outposts of the limbic system, by virtue of their connections with subcortical structures that regulate emotion and motivation. In fact, they are involved in sensory and cognitive, as well as affective, functions. These regions include tissue lacking the six cell layers characteristic of the "neocortex" that makes up the largest part of the cortical mantle, and have thus been designated as "paleocortex" or "archicortex," and as those terms suggest, homologues of some of their divisions evolved before mammals separated from other vertebrates. The fact that they are primitive, in that sense, however, does not mean they were frozen in evolutionary time. In fact, major changes in limbic cortex organization occurred in primate evolution, including changes in the hominoid and human lineages (Barger et al., 2014; Preuss, 2007).

The insula, an island of cortex buried within the lateral sulcus of primates, includes multiple divisions and a diversity of functions, including interoceptive and exteroceptive sensory functions and cognition (reviewed by Nieuwenhuys, 2012). The anterior portions have been proposed to be crucial loci in the representation of the self, social cognition, and conscious awareness (eg, Allman et al., 2011; Craig, 2011; Seeley et al., 2012). The anterior insula contains a distinctive histological division in apes and humans, the frontoinsular region, marked by the presence of a characteristic cell type, the large spindle cells, or Von Economo (VE) neurons, and is reported to be differentially enlarged in apes and humans (Bauernfeind et al., 2013). The anterior insula is connected with other limbic regions, including the anterior cingulate cortex, and Mantini et al. (2013) indicate these regions are more strongly coupled functionally in humans than in macaques.

Like the insula, the cingulate cortex is composed of multiple divisions, with diverse functions (eg, Torta and Cauda, 2011; Vogt, 2005). As indicated in Brodmann's (1909) maps of humans and monkeys, humans have a prominent superior limb of the prelimbic area (area 32), that extends posteriorly over the anterior cingulate area (area 24). Based on differences in neurochemistry, Vogt et al. (2013) indicate that this region contains two subdivisions in humans, areas d32 and 32′, that are not present in macaque monkeys, rats, or mice. This is extremely interesting, given the participation of this region in representing mental states and in other social-cognitive functions (eg, Abu-Akel and Shamay-Tsoory, 2011; Gobbini et al., 2007; Masten et al., 2011). The status of chimpanzees is, again, unknown.

Microstructural Changes

Within the neuroscience community, there have long been those who believe that the microstructure of the cortex—its cellular and laminar organization, and its intrinsic connectivity—are basically uniform across cortical areas and across species (a landmark statement of this position can be found in Rockel et al., 1980). Consistent with this, Crick and Jones (1993), allowed that humans were likely to possess cortical areas that other animals lack, and also differences in extrinsic connectivity, but gave short shrift to specializations of microstructure. Nevertheless, evidence for such differences across mammalian species, and among primates, has accumulated steadily (Charvet et al., 2015; Collins, 2011; Herculano-Houzel et al., 2008; Hof and Sherwood, 2005; Preuss, 1995, 2001). This, plus the evidence that homologous areas differ in function between humans and nonhuman primates, means there is a high probability that humans evolved specializations of cortical microstructure.

Nevertheless, given the prevailing Zeitgeist, and because the tissue required for these studies can be difficult to obtain from humans and apes (even though useful tissue can be obtained from human autopsies and from animals that die of natural causes), dedicated studies of human microstructural specializations are of fairly recent vintage. One of the first concerned the VE neurons (spindle cells) introduced earlier in this chapter. These were described initially as a unique population of large neurons in the anterior cingulate cortex of great apes and humans (Nimchinsky et al., 1999), and later in the frontoinsular cortex (for reviews, see Allman et al., 2005; Seeley et al., 2012). VE cells were said to be especially large and numerous in humans. Although it is difficult to trace the connections of individual neurons in humans, it was speculated (reasonably) that these cells have long connections, facilitating rapid cortico-cortical communication of socially relevant

information (Allman et al., 2005). Subsequently, the comparative-anatomical claim has been qualified, as similar neurons, in similar locations, have been described in a wider variety of primate species, as well as in some non-primate mammals, including large-brained animals with complex social systems, such as elephants and cetaceans (Butti et al., 2013). It remains the case, however, that humans have an unusually prominent VE cell population compared to most other primates, and the areas where they are found are important in social cognition and emotional regulation.

There is additional indication of human or hominoid specializations at the level of cell phenotypes. Among mammals, there is considerable diversity in the biochemistry and morphology of the major cortical neuron classes, namely, pyramidal cells, which form long, excitatory connections, and the predominantly short-axoned, inhibitory interneurons (Hof and Sherwood, 2007). There is evidence that humans or hominoids have specialized phenotypes of both cell classes (del Río and DeFelipe, 1997; Hof et al., 2001). In addition, an important series of studies by Raghanti, Sherwood, and their collaborators has highlighted variation among hominoid primates in the laminar distribution of axon terminals and terminal morphology in the cortex arising from deep structures that express major neurotransmitters and neuromodulators such as acetylcholine, dopamine, and serotonin (Raghanti et al., 2007, 2008a,b). In addition, they have documented differences in the distribution of interneuron classes and their intracortical connections (Raghanti et al., 2014, 2009, 2010). These workers also suggest that the greater width of neuronal minicolumns in some cortical areas in humans compared to chimpanzees and other primates, reflects species differences in innervation of the cortex by acetylcholine-containing neurons in the basal forebrain, and possibly of a specific class of interneurons (calbindin-expressing double-bouquet cells) that may be important in organizing minicolumn structure (Raghanti et al., 2010).

Perhaps the most thoroughly explored cortical area, from a comparative microstructural standpoint, is the primary visual area, V1, which exhibits both hominoid and human specializations of cellular morphology, biochemistry, and connectivity. In most New World and Old World monkeys, visual inputs to V1 from the main visual nucleus of the thalamus, the lateral geniculate nucleus, terminate in two main bands in the middle layers of cortex, termed layers 4A and 4C. Although it is difficult to directly study connections at this level of organization in apes and humans, there are reliable chemical markers for geniculate synapses in the cortex, and studies with those markers indicate that geniculate projections to layer 4A were lost in hominoid evolution (Bryant et al., 2012; Preuss et al., 1999). Also, in great apes and humans, and unlike monkeys, layer 4A is densely packed with small cells that express calbindin. In humans, furthermore, the calbindin cells are segregated into clusters separated by bands of cell bodies and dendrites that label with antibody Cat-301 (Preuss and Coleman, 2002). As Cat-301 is a marker for the so-called "magnocellular" pathway, a visual subsystem important in motion processing, Preuss and colleagues have suggested that humans underwent changes in motion sensitivity at early stages of visual processing, and that these might contribute to the differences reported in extrastriate cortex and the IPS.

Cellular specializations are not limited to neurons: there is evidence for phyletic diversity in glial cells, once considered to be merely structural and metabolic supporters of neurons, but increasingly seen as active partners in the information-processing business of the brain (Fields et al., 2014). Differences have been described between mammals orders in the morphology and physiology of astrocytes, a major class of glia (Colombo et al., 2000). Also, humans and chimpanzees, but not monkeys, reportedly possess a class of astrocytes residing in the deepest cortical layers that have long, horizontal processes studded with varicosities (Oberheim et al., 2009).

MOLECULAR SPECIALIZATIONS RELEVANT TO HUMAN BRAIN EVOLUTION

In the years since King and Wilson (1975) published their landmark review highlighting the similarities of human and chimpanzee gene and protein sequences, and the likely evolutionary importance of changes in gene expression, our knowledge of the genome and mechanisms of genetic regulation has grown immensely, and the methods available for probing species differences in molecular biology greatly improved. Sequencing genomes can now be done rapidly and cheaply; we can survey the set of transcribed genes (messenger RNAs) in tissue samples using gene chips (microarrays) or by resequencing the transcripts; and mass spectrometry is coming of age as a tool for identifying and quantifying the molecular composition of tissue samples.

The results have made it clear that the molecular differences between humans and other primates are much more extensive than the analysis of King and Wilson would lead one to expect (for review, see Preuss, 2011). While it is true that the protein-coding sequences of humans and chimpanzees are the same at about 98% of nucleotide positions, when noncoding DNA is included, overall DNA sequence similarity is much lower. In the human lineage, thousands of genes underwent evolutionary changes in expression level (ie, in the number of transcripts produced) and hundreds of genes, at least, show evidence of having undergone positive selection. Genes that underwent positive selection include a number that code for

transcription factors (TFs), proteins that bind to noncoding DNA sequences that regulate gene expression. The DNA regulation sites themselves underwent changes that affect TF binding and methylation state, another regulator of gene expression. There were changes in microRNAs, a class of molecules (unknown in 1975) that regulate the translation of RNA transcripts to proteins. Perhaps most surprisingly, evolution has produced some species-specific genes, including human-specific and chimpanzee-specific genes. Bear in mind, too, that these differences in nucleic acids may reflect only a relatively small fraction of the molecular differences between humans and chimpanzees, as proteins, lipids, and other classes of molecules have yet to be comprehensively surveyed (Bauernfeind et al., 2015a).

The tremendous number and diversity of human molecular specializations presents a problem: How do we relate changes in genes and other macromolecules to visible phenotypic changes? If the genetic changes merely affected a small number of regulatory genes—TFs, for example—one could imagine telling a reasonable story about its phenotypic consequences, based perhaps on correlations between polymorphisms in the TF sequence and variations in phenotypes. But the situation is not so simple: even when we have genes that seem to have a strong relationship to a particular phenotype, it is very difficult, given our current research methodologies, to nail down the causal connection.

A case in point is *FOXP2*, a gene that codes for a TF and that may be related to the evolution of language. *FOXP2* is regarded as a language gene because individuals in a family in England who share a loss-of-function mutation of the gene have marked language deficits, as well as some other, possibly less obvious cognitive and behavioral deficits (Vargha-Khadem et al., 1995). The *FOXP2* gene and protein sequences are highly conserved among primates, but two amino acid substitutions occurred in the human lineage, an amount of change much greater than expected based on chance (Enard et al., 2002a). This prompted the suggestion that the amino acid changes in the human lineage were the result of natural selection related to the evolution of language (Enard, Przeworski, et al., 2002). Although this is a plausible suggestion, a direct demonstration of the connection has proven elusive. What sort of ethical experimental manipulation of a gene could demonstrate its role in language? One approach adopted was to engineer a transgenic mouse that expresses a humanized *FOXP2* sequence (Enard et al., 2009; Hammerschmidt et al., 2015; Reimers-Kipping et al., 2011). As pups, these mice exhibit changes in their ultrasonic vocalizations and changes in the morphology and physiology of neurons in the basal ganglia, a structure that, in humans, is involved in language. It is not obvious, however, that mouse vocalizations have a specific relationship to human language, and the basal ganglia is involved in many functions other than language. Another approach has been to engineer humanized and "chimpanized" *FOXP2* genes and express them in cell culture to determine the suite of genes regulated by the TF product of *FOXP2* (Konopka et al., 2009). This demonstrated that *FOXP2* protein regulates numerous genes involved in neural development, and that the sets of genes regulated by the human and chimpanzee versions of FOXP2 are not identical. Furthermore, in humans, *FOXP2* is a key gene in a cluster of genes that covary in expression in a human-specific manner—a gene-expression module, as these are known (Konopka et al., 2012). Certainly, it is possible that such differences are related to language, but again, there is no smoking gun. It is, plainly, difficult to relate changes in human genetics to language or other human-specific macrophenotypes using the standard tools of molecular biology, such as transgenic mice and cell culture. New methods are needed.

Stem-cell technology offers intriguing possibilities. Using embryonic stem cells, or stem cells de-differentiated from mature cells (induced pluripotent stem cells, or iPSCs), one can generate a variety of species-specific cell types, including different types of neurons and glia from specific brain regions. The cells are grown in a dish, and under appropriate conditions, they exhibit patterns of gene expression, growth, and mature morphology that resemble their counterparts in natural tissue. Multiple cell types can be cultured together, and can organize themselves spatially in ways that reproduce some of the architectural features of normal tissue: "cortex in a dish," as it has been called (Gaspard et al., 2009), or "cerebral organoids" (Lancaster et al., 2013). The process of organization can even resemble the sequence of events in normal neurodevelopment (Eiraku et al., 2008). Cultures could be experimentally manipulated: for example, one might express humanized transgenes in chimpanzee neurons. Just how far we can go in building brain tissue in vitro is uncertain, but it might be possible to reproduce many aspects of development, histology, and physiology with these technologies. These technologies have attracted great interest for their potential tools for elucidating the mechanisms of neurological disease, but they could also be valuable for understanding human brain evolution (Hrvoj-Mihic et al., 2014).

If comparative molecular studies have so far failed to yield much insight into the evolution of language, or other conspicuous phenotypes, they have nonetheless opened our eyes to possible human specializations of cell biology, physiology, and postnatal development (Preuss, 2012b; Varki et al., 2008). Among the genes identified as undergoing increased expression in human cortex in early comparative studies of gene expression (Cáceres et al., 2003; Enard et al., 2002a; Uddin et al., 2004) are several involved in cerebral energy metabolism and synaptic plasticity, suggesting that selection promoted increased

levels of brain physiological activity in humans (Cáceres et al., 2003; Caceres et al., 2007; Preuss, 2004). Recent studies, with better data, support this idea (Bauernfeind et al., 2015a; Fu et al., 2011). Intriguingly, there was also a high rate of evolutionary changes of brain-enriched lipid elements in the human cerebral cortex (but not cerebellum), with corresponding changes in the expression of genes for lipid-related enzymes (Bozek et al., 2015). As brains are largely lipid, these results suggest an extensive reorganization or remodeling of brain membrane structure in human evolution.

There is evidence of important evolutionary changes in other molecular systems. Konopka et al. (2012), using next-generation sequencing to compare the transcriptomes of humans, chimpanzees, and macaques, identified a number of human-unique gene-expression modules in the prefrontal cortex in addition to the one that includes *FOXP2*. This suggests that systems of gene and protein interaction were reorganized in the evolution of human association cortex.

Recent studies point to evolutionary changes in the timing of gene and protein expression in the human brain. Somel et al. (2009) identified a subset of gene and protein products in the prefrontal cortex that are expressed earlier in postnatal development in humans than in chimpanzees and macaques, a phenomenon they refer to as "transcriptional neoteny." Genes involved in growth and development were especially abundant in this set. Interestingly, there is also evidence from gene expression studies (Arora et al., 2009; Bauernfeind et al., 2015b), backed by experimental studies in cell culture (Arora et al., 2012), for inhibition of programmed cell death (apoptosis) in humans. Inhibition of apoptosis could conceivably play a role in increasing brain size in early development, but it could also help preserve neurons over the course of the long human lifespan. Like other primates, all the neocortical neurons we humans possess are generated prenatally (Bhardwaj et al., 2006), but humans have evolved an extended lifespan potential—decades longer than other primates (Blurton Jones et al., 2002)—so we most likely have evolved enhanced mechanisms for preserving our neurons.

CONCLUSIONS

In summary, the currently available evidence allows us to conclude with some confidence that human brain evolution entailed the enlargement of association cortex, modifications of the long-distance, cortico-cortical connectivity, and modification of the intrinsic, microstructural organization of cortical areas. Change was not restricted to association cortex, but also involved primary and secondary sensory areas and limbic cortex. (Motor systems have not been extensively investigated.) In addition, there were major modifications of molecular systems that imply important changes not only in brain development, but also in cellular physiology. There is currently no definitive evidence for human-unique cortical areas, although the possibility cannot be excluded, and there can be no principled objection to this possibility, given some of the human-macaque differences discussed above, as well as the evidence that new areas evolved at other points in primate history (Preuss, 2007). That said, current evidence suggests that cortical expansion mainly involved enlargement of existing areas, along with modifications of their extrinsic, network connectivity, and their intrinsic architecture.

Classical accounts of human brain evolution that emphasized the enlargement of prefrontal and other regions of the association cortex, with accompanying modification of cognitive functioning, capture an important truth, but there was too much going on in other systems to be dismissed as unimportant. Moreover, changes in the intrinsic organization of brain structures, and in the morphology, biochemistry, and physiology of brain cells—changes at levels of organization few would have suspected are important in human brain evolution—must have profound effects on function. Human brains are thus not simply scaled-up ape or monkey brains: they are rife with differences in virtually every system that has been examined in detail to date, and at virtually every level of organization, from the genome up. It seems unlikely that most of these differences can be accounted for by a small set of genetic changes, although of course some changes must have had bigger effects than others. Rather, human brain evolution probably involved many episodes of selection, acting on many different systems. Even if selection targeted a particular structure or system, the result might have been general enlargement of the nonprimary cortex, as suggested by Finlay and Darlington (1995), but it is difficult at present to see how one can explain the extensive changes in the network organization of areas and changes at finer levels of organization without more particularistic accounts.

What might the future of human brain evolutionary studies offer? Clearly, it is important to have more detailed and comprehensive brain maps of chimpanzees and other great apes, comparable to maps currently available for macaques and currently in development for humans. These are necessary to identify homologous areas across species, an essential first step for a variety of critical analyses. These analyses include: determining the extent to which evolution modified the sizes of individual areas; identifying networks of cortical areas and assessing changes in their cortico-cortical connectivity; and localizing targets for assessing changes in intrinsic areal organization. Producing these maps is within the capabilities of current imaging and histological

techniques, as are many of the analyses they would support. More detailed investigations of cortical intrinsic organization would, however, benefit greatly from higher-resolution imaging than is commonly employed at present.

Another priority is improving our understanding of the chronology of human brain evolution, that is, determining when in human prehistory particular changes in the internal organization of the brain occurred, and relating those to changes in behavior, as inferred from archeology. Strengthening the ties between paleoneurology and neuroanatomy would help: if it were the case, for example, that changes in internal skull morphology reflect changes in brain shape, rather than vice versa, then it should be possible to infer changes in the proportions of different cortical regions from changes in brain shape (Bruner et al., 2016). Genetic approaches might take us further, if we could tie specific anatomical and physiological changes to specific genetic changes, and if we could date those genetic changes, which is possible in some cases based on linkage disequilibrium. If this were to prove practical, it could inform us about changes at multiple levels of organization. By combining this approach with stem-cell (Hrvoj-Mihic et al., 2014) and embryonic tissue-culture techniques (Letinic and Rakic, 2001), it might even be possible to recreate features of ancestral brain organization in a dish.

It is vital to appreciate that all these advances—even the modest ones—require the continued study of chimpanzees and other great apes. We are fortunate to now have a variety of noninvasive methods for studying apes. Yet the animals themselves are likely to be the critical limiting resources in the future, given the decreasing numbers of great apes in captivity and the likelihood they will become extinct in the wild over the next several decades (Povinelli and Preuss, 2012). The future of human brain evolution studies, and indeed of scientific approaches to human nature generally, depends critically on the preservation of great apes.

ACKNOWLEDGMENTS

This work is supported by National Institutes of Health Office of Research Infrastructure Programs/OD P51OD11132 to the Yerkes National Primate Research Center and by the John Templeton Foundation (award 40463). Human data used to generate some of the figures were provided by the Human Connectome Project, WU-Minn Consortium (principal investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657) funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and by the McDonnell Center for Systems Neuroscience at Washington University. The author is especially grateful to Matthew Glasser and Longchuan Li for processing chimpanzee and macaque imaging data through the Human Connectome Project pipeline, and to Katherine Bryant, Mary Ann Cree, and Christina Rogers for providing comments on drafts of the manuscript.

REFERENCES

Aboitiz, F., 2012. Gestures, vocalizations, and memory in language origins. Frontiers in Evolutionary Neuroscience 4, 2.

Abu-Akel, A., Shamay-Tsoory, S., 2011. Neuroanatomical and neurochemical bases of theory of mind. Neuropsychologia 49, 2971–2984.

Allen, J.S., 2009. The Lives of the Brain: Human Evolution and the Organ of Mind. Belknap Press of Harvard University Press, Cambridge, Mass.

Allman, J.M., Watson, K.K., Tetreault, N.A., Hakeem, A.Y., 2005. Intuition and autism: a possible role for Von Economo neurons. Trends in Cognitive Sciences 9, 367–373.

Allman, J.M., Tetreault, N.A., Hakeem, A.Y., Manaye, K.F., Semendeferi, K., Erwin, J.M., Park, S., Goubert, V., Hof, P.R., 2011. The von Economo neurons in the frontoinsular and anterior cingulate cortex. Annals of the New York Academy of Sciences 1225, 59–71.

Allman, J., 1982. Reconstructing the evolution of the brain in primates through the use of comparative neurophysiological and anatomical data. In: Armstrong, E., Falk, D. (Eds.), Primate Brain Evolution. Methods and Concepts. Plenum, New York, pp. 13–28.

Arbib, M.A., 2012. How the Brain Got Language: The Mirror System Hypothesis. Oxford University Press.

Armstrong, E., 1982. Mosaic Evolution in the Primate Brain: Differences and Similarities in the Hominoid Thalamus. Primate Brain Evolution. Springer, US, pp. 131–161.

Arora, G., Polavarapu, N., McDonald, J.F., 2009. Did natural selection for increased cognitive ability in humans lead to an elevated risk of cancer? Medical Hypotheses 73, 453–456.

Arora, G., Mezencev, R., McDonald, J.F., 2012. Human cells display reduced apoptotic function relative to chimpanzee cells. PLoS One 7, e46182.

Avants, B.B., Avants, B.B., Schoenemann, P.T., Schoenemann, P.T., Gee, J.C., Gee, J.C., 2006. Lagrangian frame diffeomorphic image registration: morphometric comparison of human and chimpanzee cortex. Medical Image Analysis 10, 397–412.

Bailey, P., von Bonin, G., 1951. The Isocortex of Man. Univ. of Illinois Press, Urbana.

Bailey, P., von Bonin, G., McCulloch, W.S., 1950. The Isocortex of the Chimpanzee. Univ. of Illinois Press, Urbana, IL.

Balsters, J.H., Cussans, E., Diedrichsen, J., Phillips, K.A., Preuss, T.M., Rilling, J.K., Ramnani, N., 2010. Evolution of the cerebellar cortex: the selective expansion of prefrontal-projecting cerebellar lobules. NeuroImage 49, 2045–2052.

Barger, N., Hanson, K.L., Teffer, K., Schenker-Ahmed, N.M., Semendeferi, K., 2014. Evidence for evolutionary specialization in human limbic structures. Frontiers in Human Neuroscience 277.

Barks, S.K., Calhoun, M.E., Hopkins, W.D., Cranfield, M.R., Mudakikwa, A., Stoinski, T.S., Patterson, F.G., Erwin, J.M., Hecht, E.E., Hof, P.R., Sherwood, C.C., 2015a. Brain organization of gorillas reflects species differences in ecology. American Journal of Physical Anthropology 156, 252–262.

Barks, S.K., Parr, L.A., Rilling, J.K., 2015b. The default mode network in chimpanzees (*Pan troglodytes*) is similar to that of humans. Cerebral Cortex 25, 538–544.

Barton, R.A., Venditti, C., 2013. Human frontal lobes are not relatively large. Proceedings of the National Academy of Sciences of the United States of America 110, 9001–9006.

Bauernfeind, A.L., de Sousa, A.A., Avasthi, T., Dobson, S.D., Raghanti, M.A., Lewandowski, A.H., Zilles, K., Semendeferi, K., Allman, J.M., Craig, A.D.B., Hof, P.R., Sherwood, C.C., 2013. A volumetric comparison of the insular cortex and its subregions in primates. Journal of Human Evolution 64, 263–279.

Bauernfeind, A.L., Reyzer, M.L., Caprioli, R.M., Ely, J.J., Babbitt, C.C., Wray, G.A., Hof, P.R., Sherwood, C.C., 2015a. High spatial resolution proteomic comparison of the brain in humans and chimpanzees. Journal of Comparative Neurology 523, 2043–2061.

Bauernfeind, A.L., Soderblom, E.J., Turner, M.E., Moseley, M.A., Ely, J.J., Hof, P.R., Sherwood, C.C., Wray, G.A., Babbitt, C.C., 2015b. Evolutionary divergence of gene and potein expression in the brains of humans and chimpanzees. Genome Biology and Evolution 7, 2276–2288.

Bhardwaj, R.D., Curtis, M.A., Spalding, K.L., Buchholz, B.A., Fink, D., Björk-Eriksson, T., Nordborg, C., Gage, F.H., Druid, H., Eriksson, P.S., Frisén, J., 2006. Neocortical neurogenesis in humans is restricted to development. Proceedings of the National Academy of Sciences of the United States of America 103, 12564–12568.

Blinkov, S., Glezer, I., 1968. The Human Brain in Figures and Tables. Basic Books, New York.

Blurton Jones, N.G., Hawkes, K., O'Connell, J.F., 2002. Antiquity of postreproductive life: are there modern impacts on hunter-gatherer postreproductive life spans? American Journal of Human Biology 14, 184–205.

von Bonin, G., Bailey, P., 1947. The Neocortex of Macaca Mulatta. University of Illinois Press, Urbana.

von Bonin, G., Bailey, P., 1961. Patterns of the cerebral isocortex. In: Hofer, H., Schultz, A.H., Starck, D. (Eds.), Primatologia. S. Karger, Basel, pp. 1–42.

von Bonin, G., 1944. The architecture. In: Bucy, P.C. (Ed.), The Precentral Motor Cortex. University of Illinois Press, Urbana, IL, pp. 7–82.

Bozek, K., Wei, Y., Yan, Z., Liu, X., Xiong, J., Sugimoto, M., Tomita, M., Pääbo, S., Sherwood, C.C., Hof, P.R., Ely, J.J., Li, Y., Steinhauser, D., Willmitzer, L., Giavalisco, P., Khaitovich, P., 2015. Organization and evolution of brain lipidome revealed by large-scale analysis of human, chimpanzee, macaque, and mouse tissues. Neuron 85, 695–702.

Broadfield, D.C., Holloway, R.L., 2010. The Human Brain Evolving: Paleoneurological Studies in Honor of Ralph L. Holloway. Stone Age Institute Press, Gosport, IN.

Brodmann, K., 1909. Vergleichende Lokalisationslehre der Grosshirnrhinde. Barth (reprinted as Brodmann's 'Localisation in the Cerebral Cortex,' translated and edited by L. J. Garey, London: Smith-Gordon, 1994).

Brodmann, K., 1912. Neue Ergibnisse uber die vergleichende histologische Lokalisation der Grosshirnrinde mit besonderer Berucksichtigung des Stirnhirns. Anatomischer Anzeiger 41 (Suppl.), 157–216.

Bruner, E., Preuss, T.M., Chen, X., Rilling, J.K., 2016. Evidence for expansion of the precuneus in human evolution. Brain Structure and Function 1–10.

Bruner, E., 2004. Geometric morphometrics and paleoneurology: brain shape evolution in the genus *Homo*. Journal of Human Evolution 47, 279–303.

Bryant, K.L., Suwyn, C., Reding, K.M., Smiley, J.F., Hackett, T.A., Preuss, T.M., 2012. Evidence for ape and human specializations in geniculostriate projections from VGLUT2 immunohistochemistry. Brain, Behaviour and Evolution 80, 210–221.

Buccino, G., Binkofski, F., Fink, G.R., Fadiga, L., Fogassi, L., Gallese, V., Seitz, R.J., Zilles, K., Rizzolatti, G., Freund, H.J., 2001. Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study. European Journal of Neuroscience 13, 400–404.

Buckner, R.L., Carroll, D.C., 2007. Self-projection and the brain. Trends in Cognitive Sciences 11, 49–57.

Buckner, R.L., Sepulcre, J., Talukdar, T., Krienen, F.M., Liu, H., Hedden, T., Andrews-Hanna, J.R., Sperling, R.A., Johnson, K.A., 2009. Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's Disease. The Journal of Neuroscience 29, 1860–1873.

Buckner, R.L., 2012. The serendipitous discovery of the brain's default network. NeuroImage 62, 1137–1145.

Bush, E.C., Allman, J.M., 2004. The scaling of frontal cortex in primates and carnivores. Proceedings of the National Academy of Sciences of the United States of America 101, 3962–3966.

Butti, C., Santos, M., Uppal, N., Hof, P.R., 2013. Von Economo neurons: clinical and evolutionary perspectives. Cortex 49, 312–326.

Buxhoeveden, D.P., Switala, A.E., Litaker, M., 2001. Lateralization of minicolumns in human planum temporale is absent in nonhuman primate cortex. Brain, Behaviour and Evolution 57 (6), 349–358.

Cáceres, M., Lachuer, J., Zapala, M.A., Redmond, J., Kudo, L., Geschwind, D., Lockhart, D., Preuss, T., Barlow, C., 2003. Elevated gene expression levels distinguish human from non-human primate brains. Proceedings of the National Academy of Sciences of the United States of America 100, 1330–1335.

Caceres, M., Suwyn, C., Maddox, M., Thomas, J.W., Preuss, T.M., 2007. Increased cortical expression of two synaptogenic thrombospondins in human brain evolution. Cerebral Cortex 17, 2312–2321.

Cantalupo, C., Oliver, J., Smith, J., Nir, T., Taglialatela, J.P., Hopkins, W.D., 2009. The chimpanzee brain shows human-like perisylvian asymmetries in white matter. European Journal of Neuroscience 30, 431–438.

Charvet, C.J., Cahalane, D.J., Finlay, B.L., 2015. Systematic, cross-cortex variation in neuron numbers in rodents and primates. Cerebral Cortex 25, 147–160.

Cohen, J., 2010. Almost Chimpanzee: Searching for What Makes Us Human, in Rainforests, Labs, Sanctuaries, and Zoos, first ed. Times Books, New York.

Collins, C.E., 2011. Variability in neuron densities across the cortical sheet in primates. Brain, Behaviour and Evolution 78, 37–50.

Colombo, J.A., Fuchs, E., Härtig, W., Marotte, L.R., Puissant, V., 2000. "Rodent-like" and & "primate-like" types of astroglial architecture in the adult cerebral cortex of mammals: a comparative study. Anatomy and Embryology 201, 111–120.

Craig, A.D.B., 2011. Significance of the insula for the evolution of human awareness of feelings from the body. Annals of the New York Academy of Sciences 1225, 72–82.

Crick, F., Jones, E., 1993. Backwardness of human neuroanatomy. Nature 361, 109–110.

Darwin, C., 1871. The Descent of Man, and Selection in Relation to Sex. John Murray [Facsimile edition: Princeton, NJ: Princeton University Press, 1981], London.

de Sousa, A., Cunha, E., 2012. Hominins and the Emergence of the Modern Human Brain, first ed. Elsevier B.V, pp. 293–322.

de Sousa, A., Wood, B., 2007. The hominin fossil record and the emergence of the modern human central nervous system. In: Kaas, J.H.,

Preuss, T.M. (Eds.), Evolution of Nervous Systems, Primates, vol. 4. Elsevier, Oxford, pp. 291–336.

Deacon, T.W., 1997. The Symbolic Species: The Co-evolution of Language and the Brain, first ed. W.W. Norton.

Deacon, T.W., 2006. The Evolution of Language Systems in the Human Brain, pp. 1–19.

del Río, M.R., DeFelipe, J., 1997. Colocalization of parvalbumin and calbindin D-28k in neurons including chandelier cells of the human temporal neocortex. Journal of Chemical Neuroanatomy 12, 165–173.

Denys, K., Vanduffel, W., Fize, D., Nelissen, K., Sawamura, H., Georgieva, S., Vogels, R., Van Essen, D., Orban, G.A., 2004. Visual activation in prefrontal cortex is stronger in monkeys than in humans. Journal of Cognitive Neuroscience 16, 1505–1516.

Diamond, J.M., 1992. The Third Chimpanzee : The Evolution and Future of the Human Animal, first ed. HarperCollins, New York, NY.

Eiraku, M., Watanabe, K., Matsuo-Takasaki, M., Kawada, M., Yonemura, S., Matsumura, M., Wataya, T., Nishiyama, A., Muguruma, K., Sasai, Y., 2008. Self-organized formation of polarized cortical tissues from ESCs and its active manipulation by extrinsic signals. Cell Stem Cell 3, 519–532.

Enard, W., Khaitovich, P., Klose, J., Zollner, S., Heissig, F., Giavalisco, P., Nieselt-Struwe, K., Muchmore, E., Varki, A., Ravid, R., Doxiadis, G.M., Bontrop, R.E., Paabo, S., 2002a. Intra- and interspecific variation in primate gene expression patterns. Science 296, 340–343.

Enard, W., Przeworski, M., Fisher, S.E., Lai, C.S.L., Wiebe, V., Kitano, T., Monaco, A.P., Pääbo, S., 2002b. Molecular evolution of *FOXP2*, a gene involved in speech and language. Nature 418, 869–872.

Enard, W., Gehre, S., Hammerschmidt, K., Hölter, S.M., Blass, T., Somel, M., Brückner, M.K., Schreiweis, C., Winter, C., Sohr, R., Becker, L., Wiebe, V., Nickel, B., Giger, T., Müller, U., Groszer, M., Adler, T., Aguilar, A., Bolle, I., Calzada-Wack, J., Dalke, C., Ehrhardt, N., Favor, J., Fuchs, H., Gailus-Durner, V., Hans, W., Hölzlwimmer, G., Javaheri, A., Kalaydjiev, S., Kallnik, M., Kling, E., Kunder, S., Mossbrugger, I., Naton, B., Racz, I., Rathkolb, B., Rozman, J., Schrewe, A., Busch, D.H., Graw, J., Ivandic, B., Klingenspor, M., Klopstock, T., Ollert, M., Quintanilla-Martinez, L., Schulz, H., Wolf, E., Wurst, W., Zimmer, A., Fisher, S.E., Morgenstern, R., Arendt, T., Hrabé de Angelis, M., Fischer, J., Schwarz, J., Pääbo, S., 2009. A humanized version of Foxp2 affects cortico-basal ganglia circuits in mice. Cell 137, 961–971.

Falk, D., 1980. A reanalysis of the South African australopithecine natural endocasts. American Journal of Physical Anthropology 53, 525–539.

Falk, D., 2014. Interpreting sulci on hominin endocasts: old hypotheses and new findings. Frontiers in Human Neuroscience 134.

Falk, D., 2015. Evolution of the primate brain. In: Henke, W., Tattersall, I. (Eds.), Handbook of Paleoanthropology. Springer, Berlin Heidelberg, pp. 1495–1525.

Fields, R.D., Araque, A., Johansen-Berg, H., Lim, S.-S., Lynch, G., Nave, K.-A., Nedergaard, M., Perez, R., Sejnowski, T., Wake, H., 2014. Glial biology in learning and cognition. Neuroscientist 20, 426–431.

Finlay, B.L., Darlington, R.B., 1995. Linked regularities in the development and evolution of mammalian brains. Science 268, 1578–1584.

Fu, X., Giavalisco, P., Liu, X., Catchpole, G., Fu, N., Ning, Z.-B., Guo, S., Yan, Z., Somel, M., Pääbo, S., Zeng, R., Willmitzer, L., Khaitovich, P., 2011. Rapid metabolic evolution in human prefrontal cortex. Proceedings of the National Academy of Sciences of the United States of America 108, 6181–6186.

Gannon, P.J., Holloway, R.L., Broadfield, D.C., Braun, A.R., 1998. Asymmetry of chimpanzee planum temporale: humanlike pattern of Wernicke's brain language area homolog. Science 279, 220–222.

Gaspard, N., Gaillard, A., Vanderhaeghen, P., 2009. Making cortex in a dish: in vitro corticopoiesis from embryonic stem cells. Cell Cycle 8, 2491–2496.

Gazzaniga, M.S., 2008. Human: The Science Behind What Makes Us Unique. Ecco, New York.

Geschwind, N., Levitsky, W., 1968. Human brain: left-right asymmetries in temporal speech region. Science 161, 186–187.

Geschwind, N., 1970. The organization of language and the brain. Science 170, 940–944.

Ghazanfar, A.A., Miller, C.T., 2006. Language evolution: loquacious monkey brains? Current Biology 16, R879–R881.

Gilissen, E.P., Hopkins, W.D., 2013. Asymmetries of the parietal operculum in chimpanzees (*Pan troglodytes*) in relation to handedness for tool use. Cerebral Cortex 23, 411–422.

Glasser, M.F., Van Essen, D.C., 2011. Mapping human cortical areas in vivo based on myelin content as revealed by T1- and T2-weighted MRI. The Journal of Neuroscience 31, 11597–11616.

Glasser, M.F., Goyal, M.S., Preuss, T.M., Raichle, M.E., Van Essen, D.C., 2014. Trends and properties of human cerebral cortex: correlations with cortical myelin content. NeuroImage 93 (Pt 2), 165–175.

Gobbini, M.I., Koralek, A.C., Bryan, R.E., Montgomery, K.J., Haxby, J.V., 2007. Two takes on the social brain: a comparison of theory of mind tasks. Journal of Cognitive Neuroscience 19, 1803–1814.

Goldman-Rakic, P.S., 1988. Topography of cognition: parallel distributed networks in primate association cortex. Annual Review Neuroscience 11, 137–156.

Goodman, M., Porter, C.A., Czelusniak, J., Page, S.L., Schneider, H., Shoshani, J., Gunnell, G., Groves, C.P., 1998. Toward a phylogenetic classification of primates based on DNA evidence complemented by fossil evidence. Molecular Phylogenetics and Evolution 9, 585–598.

Gould, S.J., 1977. Ontogeny and Phylogeny. Belknap Press of Harvard University Press, Cambridge, Mass.

Hammerschmidt, K., Schreiweis, C., Minge, C., Paabo, S., Fischer, J., Enard, W., 2015. A humanized version of Foxp2 does not affect ultrasonic vocalization in adult mice. Genes, Brain and Behavior 14, 583–590.

Hecht, E.E., Murphy, L.E., Gutman, D.A., Votaw, J.R., Schuster, D.M., Preuss, T.M., Orban, G.A., Stout, D., Parr, L.A., 2013. Differences in neural activation for object-directed grasping in chimpanzees and humans. The Journal of Neuroscience 33, 14117–14134.

Hecht, E.E., Gutman, D.A., Bradley, B.A., Preuss, T.M., Stout, D., 2015a. Virtual dissection and comparative connectivity of the superior longitudinal fasciculus in chimpanzees and humans. NeuroImage 108, 124–137.

Hecht, E.E., Gutman, D.A., Khreisheh, N., Taylor, S.V., Kilner, J., Faisal, A.A., Bradley, B.A., Chaminade, T., Stout, D., 2015b. Acquisition of Paleolithic toolmaking abilities involves structural remodeling to inferior frontoparietal regions. Brain Structure and Function 220, 2315–2331.

Henrich, J., 2015. The Secret of Our Success: How Culture Is Driving Human Evolution, Domesticating Our Species, and Making Us Smarter, first ed. Princeton University Press, Princeton, NJ.

Herculano-Houzel, S., Collins, C.E., Wong, P., Kaas, J.H., Lent, R., 2008. The basic nonuniformity of the cerebral cortex. Proceedings of the National Academy of Sciences of the United States of America 105, 12593−12598.

Herndon, J.G., Tigges, J., Klumpp, S.A., Anderson, D.C., 1998. Brain weight does not decrease with age in adult rhesus monkeys. Neurobiology of Aging 19, 267−272.

Hof, P.R., Sherwood, C.C., 2005. Morphomolecular neuronal phenotypes in the neocortex reflect phylogenetic relationships among certain mammalian orders. The Anatomical Record. Part A, Discoveries in Molecular, Cellular, and Evolutionary Biology 287, 1153−1163.

Hof, P.R., Sherwood, C.C., 2007. The evolution of neuron classes in the neocortex of mammals. In: Kaas, J.H., Krubitzer, L.A. (Eds.), Evolution of Nervous Systems, Mammals, vol. 3. Elsevier, Oxford, pp. 113−124.

Hof, P.R., Nimchinsky, E.A., Perl, D.P., Erwin, J.M., 2001. An unusual population of pyramidal neurons in the anterior cingulate cortex of hominids contains the calcium-binding protein calretinin. Neuroscience Letters 307, 139−142.

Holloway, R.L., de la Coste-Lareymondie, M.C., 1982. Brain endocast asymmetry in pongids and hominids: some preliminary findings on the paleontology of cerebral dominance. American Journal of Physical Anthropology 58, 101−110.

Holloway, R.L., Sherwood, C.C., Hof, P.R., Rilling, J.K., 2009. Evolution of the Brain in Humans − Paleoneurology, Encyclopedia of Neuroscience. Springer Berlin Heidelberg, pp. 1326−1334.

Holloway, R.L., 1966. Cranial capacity, neural reorganization, and hominid evolution: a search for more suitable parameters. American Anthropologist 68, 103−121.

Holloway, R.L., 1981. Revisiting the South African Taung australopithecine endocast: the position of the lunate sulcus as determined by the stereoplotting technique. American Journal of Physical Anthropology 56, 43−58.

Holloway, R.L., 2002. Brief communication: how much larger is the relative volume of area 10 of the prefrontal cortex in humans? American Journal of Physical Anthropology 118, 399−401.

Holloway, R.L., 2008. The human brain evolving: a personal retrospective. Annual Review of Anthropology 37, 1−19.

Hopkins, W.D., Marino, L., 2000. Asymmetries in cerebral width in nonhuman primate brains as revealed by magnetic resonance imaging (MRI). Neuropsychologia 38, 493−499.

Hopkins, W.D., Nir, T.M., 2010. Planum temporale surface area and grey matter asymmetries in chimpanzees (*Pan troglodytes*): the effect of handedness and comparison with findings in humans. Behavioural Brain Research 208, 436−443.

Hopkins, W.D., Lyn, H., Cantalupo, C., 2009. Volumetric and lateralized differences in selected brain regions of chimpanzees (*Pan troglodytes*) and bonobos (*Pan paniscus*). American Journal of Primatology 71, 988−997.

Hrvoj-Mihic, B., Marchetto, M.C.N., Gage, F.H., Semendeferi, K., Muotri, A.R., 2014. Novel tools, classic techniques: evolutionary studies using primate pluripotent stem cells. Biological Psychiatry 75, 929−935.

Huxley, T.H., 1863. Evidence as to Man's Place in Nature. Williams and Norgate [1959, Ann Arbor, University of Michigan], London.

Jefferies, E., 2013. The neural basis of semantic cognition: converging evidence from neuropsychology, neuroimaging and TMS. Cortex 49, 611−625.

Jerison, H.J., 1973. Evolution of the Brain and Intelligence. Academic Press.

Jerison, H.J., 1977. Should phrenology be rediscovered? Current Anthropology 744.

Kaas, J.H., Preuss, T.M., 2007. Evolution of Nervous Systems. In: Primates, vol. 4. Elsevier, Oxford.

Kaas, J.H., Preuss, T.M., 2013. Human brain evolution. In: Squire, L., Berg, D., Bloom, F.E., du Lac, S., Ghosh, A., Spitzer, N.C. (Eds.), Fundamental Neuroscience, fourth ed. Academic Press, San Diego, CA, pp. 901−918.

Kaas, J.H., 1987. The organization and evolution of neocortex. In: Wise, S.P. (Ed.), Higher Brain Function: Recent Explorations of the Brain's Emergent Properties. John Wiley, New York, pp. 347−378.

King, M.C., Wilson, A.C., 1975. Evolution at two levels in humans and chimpanzees. Science 188, 107−116.

Kolster, H., Janssens, T., Orban, G.A., Vanduffel, W., 2014. The retinotopic organization of macaque occipitotemporal cortex anterior to V4 and caudoventral to the middle temporal (MT) cluster. The Journal of Neuroscience 34, 10168−10191.

Konopka, G., Bomar, J.M., Winden, K., Coppola, G., Jonsson, Z.O., Gao, F., Peng, S., Preuss, T.M., Wohlschlegel, J.A., Geschwind, D.H., 2009. Human-specific transcriptional regulation of CNS development genes by FOXP2. Nature 462, 213−217.

Konopka, G., Friedrich, T., Davis-Turak, J., Winden, K., Oldham, M.C., Gao, F., Chen, L., Wang, G.-Z., Luo, R., Preuss, T.M., Geschwind, D.H., 2012. Human-specific transcriptional networks in the brain. Neuron 75, 601−617.

Lancaster, M.A., Renner, M., Martin, C.-A., Wenzel, D., Bicknell, L.S., Hurles, M.E., Homfray, T., Penninger, J.M., Jackson, A.P., Knoblich, J.A., 2013. Cerebral organoids model human brain development and microcephaly. Nature 501, 373−379.

Langergraber, K.E., Prufer, K., Rowney, C., Boesch, C., Crockford, C., Fawcett, K., Inoue, E., Inoue-Muruyama, M., Mitani, J.C., Muller, M.N., Robbins, M.M., Schubert, G., Stoinski, T.S., Viola, B., Watts, D., Wittig, R.M., Wrangham, R.W., Zuberbuhler, K., Paabo, S., Vigilant, L., 2012. Generation times in wild chimpanzees and gorillas suggest earlier divergence times in great ape and human evolution. Proceedings of the National Academy of Sciences of the United States of America 109, 15716−15721.

Lashley, K.S., 1949. Persistent problems in the evolution of mind. The Quarterly Review Biology 24, 28−42.

Leigh, S.R., Shea, B.T., 1996. Ontogeny of body size variation in African apes. American Journal of Physical Anthropology 99, 43−65.

Leroy, F., Cai, Q., Bogart, S.L., Dubois, J., Coulon, O., Monzalvo, K., Fischer, C., Glasel, H., Van der Haegen, L., Bénézit, A., Lin, C.-P., Kennedy, D.N., Ihara, A.S., Hertz-Pannier, L., Moutard, M.-L., Poupon, C., Brysbaert, M., Roberts, N., Hopkins, W.D., Mangin, J.-F., Dehaene-Lambertz, G., 2015. New human-specific brain landmark: the depth asymmetry of superior temporal sulcus. Proceedings of the National Academy of Sciences of the United States of America 112, 1208−1213.

Letinic, K., Rakic, P., 2001. Telencephalic origin of human thalamic GABAergic neurons. Nature Neuroscience 4, 931−936.

Li, L., Hu, X., Preuss, T.M., Glasser, M.F., Damen, F.W., Qiu, Y., Rilling, J., 2013. Mapping putative hubs in human, chimpanzee and

rhesus macaque connectomes via diffusion tractography. NeuroImage 80, 462−474.

Liakakis, G., Nickel, J., Seitz, R.J., 2011. Diversity of the inferior frontal gyrus—A meta-analysis of neuroimaging studies. Behavioural Brain Research 225, 341−347.

Lyon, D.C., 2007. The evolution of visual cortex and visual systems. In: Kaas, J.H., Preuss, T.M. (Eds.), Evolution of Nervous Sytems, Primates, vol. 4. Elsevier, Oxford, pp. 267−306.

Mantini, D., Gerits, A., Nelissen, K., Durand, J.B., Joly, O., Simone, L., Sawamura, H., Wardak, C., Orban, G.A., Buckner, R.L., Vanduffel, W., 2011. Default mode of brain function in monkeys. The Journal of Neuroscience 31, 12954−12962.

Mantini, D., Corbetta, M., Romani, G.L., Orban, G.A., Vanduffel, W., 2013. Evolutionarily novel functional networks in the human brain? The Journal of Neuroscience 33, 3259−3275.

Mars, R.B., Jbabdi, S., Sallet, J., O'Reilly, J.X., Croxson, P.L., Olivier, E., Noonan, M.P., Bergmann, C., Mitchell, A.S., Baxter, M.G., Behrens, T.E.J., Johansen-Berg, H., Tomassini, V., Miller, K.L., Rushworth, M.F.S., 2011. Diffusion-weighted imaging tractography-based parcellation of the human parietal cortex and comparison with human and macaque resting-state functional connectivity. The Journal of Neuroscience 31, 4087−4100.

Mars, R.B., Neubert, F.-X., Noonan, M.P., Sallet, J., Toni, I., Rushworth, M.F.S., 2012. On the relationship between the "default mode network" and the "social brain". Frontiers in Human Neuroscience 189.

Mars, R.B., Sallet, J., Neubert, F.X., Rushworth, M.F.S., 2013. Connectivity profiles reveal the relationship between brain areas for social cognition in human and monkey temporoparietal cortex. Proceedings of the National Academy of Sciences of the United States of America 110, 10806−10811.

Martin, R.D., 1981. Relative brain size and basal metabolic rate in terrestrial vertebrates. Nature 57−60.

Masten, C.L., Morelli, S.A., Eisenberger, N.I., 2011. An fMRI investigation of empathy for 'social pain' and subsequent prosocial behavior. NeuroImage 55, 381−388.

Mcbrearty, S., Brooks, A.S., 2000. The revolution that wasn't: a new interpretation of the origin of modern human behavior. Journal of Human Evolution 39, 453−463.

Neubert, F.-X., Mars, R.B., Thomas, A.G., Sallet, J., Rushworth, M.F.S., 2014. Comparison of human ventral frontal cortex: areas for cognitive control and language with areas in monkey frontal cortex. Neuron 81, 700−713.

Nieuwenhuys, R., 2012. The insular cortex: a review. Progress in Brain Research 195, 123−163.

Nimchinsky, E.A., Gilissen, E., Allman, J.M., Perl, D.P., Erwin, J.M., Hof, P.R., 1999. A neuronal morphologic type unique to humans and great apes. Proceedings of the National Academy of Sciences of the United States of America 96, 5268−5273.

Oberheim, N.A., Takano, T., Han, X., He, W., Lin, J.H., Wang, F., Xu, Q., Wyatt, J.D., Pilcher, W., Ojemann, J.G., Ransom, B.R., Goldman, S.A., Nedergaard, M., 2009. Uniquely hominid features of adult human astrocytes. The Journal of Neuroscience 29, 3276−3287.

Parr, L.A., Hecht, E., Barks, S.K., Preuss, T.M., Votaw, J.R., 2009. Face processing in the chimpanzee brain. Current Biology 19, 50−53.

Parr, L.A., 2011. The evolution of face processing in primates. Philosophical Transactions of the Royal Society B: Biological Sciences 366, 1764−1777.

Passingham, R.E., Smaers, J.B., 2014. Is the prefrontal cortex especially enlarged in the human brain allometric relations and remapping factors. Brain, Behaviour and Evolution 84, 156−166.

Passingham, R.E., 1973. Anatomical differences between the neocortex of man and other primates. Brain, Behaviour and Evolution 337−359.

Passingham, R.E., 1998. The specializations of the human cerebral cortex. In: Milner, A.D. (Ed.), Comparative Neuropsychology. Oxford University Press, Oxford, pp. 271−298.

Passingham, R.E., 2002. The frontal cortex: does size matter? Nature Neuroscience 5, 190−192.

Passingham, R.E., 2008. What Is Special about the Human Brain? Oxford University Press, Oxford; New York.

Peeters, R., Simone, L., Nelissen, K., Fabbri-Destro, M., Vanduffel, W., Rizzolatti, G., Orban, G.A., 2009. The representation of tool use in humans and monkeys: common and uniquely human features. The Journal of Neuroscience 29, 11523−11539.

Peeters, R.R., Rizzolatti, G., Orban, G.A., 2013. Functional properties of the left parietal tool use region. NeuroImage 78, 83−93.

Perelman, P., Johnson, W.E., Roos, C., Seuánez, H.N., Horvath, J.E., Moreira, M.A.M., Kessing, B., Pontius, J., Roelke, M., Rumpler, Y., Schneider, M.P.C., Silva, A., O'Brien, S.J., Pecon-Slattery, J., 2011. A molecular phylogeny of living primates. PLoS Genetics 7, e1001342.

Petrides, M., Pandya, D.N., 1994. Comparative architectonic analysis of the human and the macaque frontal cortex. In: Booler, F., Grafman, J. (Eds.), Handbook of Neuropsychology. Elsevier, Amsterdam, pp. 17−58.

Pinsk, M.A., Arcaro, M., Weiner, K.S., Kalkus, J.F., Inati, S.J., Gross, C.G., Kastner, S., 2008. Neural representations of faces and body parts in macaque and human cortex: a comparative fMRI study. Journal of Neurophysiology 101, 2581−2600.

Povinelli, D.J., Eddy, T.J., 1996. What young chimpanzees know about seeing. Monographs of the Society for Research in Child Development 61 (i−vi), 1−152 discussion 153−191.

Povinelli, D., Preuss, T.M., 2012. Afterword: World without Apes? World without Weight: Perspectives on an Alien Mind. Oxford University Press, pp. 330−332.

Premack, D., 2010. Why humans are unique: three theories. Perspectives on Psychological Science 5, 22−32.

Preuss, T.M., Coleman, G.Q., 2002. Human-specific organization of primary visual cortex: alternating compartments of dense Cat-301 and calbindin immunoreactivity in layer 4A. Cerebral Cortex 12, 671−691.

Preuss, T.M., Robert, J.S., 2014. Animal models of the human brain: repairing the paradigm. In: Gazzaniga, M.S., Mangun, G. (Eds.), The Cognitive Neurosciences V. MIT Press, pp. 59−66.

Preuss, T.M., Qi, H., Kaas, J.H., 1999. Distinctive compartmental organization of human primary visual cortex. Proceedings of the National Academy of Sciences of the United States of America 96, 11601−11606.

Preuss, T.M., 1995. The argument from animals to humans in cognitive neuroscience. In: Gazzaniga, M.S. (Ed.), The Cognitive Neurosciences. MIT Press, Cambridge, MA, pp. 1227−1241.

Preuss, T.M., 2001. The discovery of cerebral diversity: an unwelcome scientific revolution. In: Falk, D., Gibson, K. (Eds.), Evolutionary Anatomy of the Primate Cerebral Cortex. Cambridge University Press, Cambridge, pp. 138−164.

Preuss, T.M., 2004. Specializations of the human visual system: the monkey model meets human reality. In: Kaas, J.H., Collins, C.E. (Eds.), The Primate Visual System. CRC Press, Boca Raton, FL, pp. 231–259.

Preuss, T.M., 2007. Primate brain evolution in phylogenetic context. In: Kaas, J.H., Preuss, T.M. (Eds.), Evolution of Nervous Systems, vol. 4: Primates. Elsevier, Oxford, pp. 1–34.

Preuss, T.M., 2010. Reinventing primate neuroscience for the twenty-first century. In: Platt, M.L., Ghazanfar, A.A. (Eds.), Primate Neuroethology. Oxford University Press, Oxford, pp. 422–454.

Preuss, T.M., 2011. The human brain: rewired and running hot. Annals of the New York Academy of Sciences 1225 (Suppl. 1), E182–E191.

Preuss, T.M., 2012a. Alien brains: a defense of exceptionalism. In: Povinelli, D.J. (Ed.), World Without Weight: Perspectives on an Alien Mind. Oxford University Press, Oxford, pp. 30–31.

Preuss, T.M., 2012b. Human brain evolution: from gene discovery to phenotype discovery. Proceedings of the National Academy of Sciences of the United States of America 109 (Suppl. 1), 10709–10716.

Price, C.J., 2012. A review and synthesis of the first 20 years of PET and fMRI studies of heard speech, spoken language and reading. NeuroImage 62, 816–847.

Raghanti, M.A., Stimpson, C.D., Marcinkiewicz, J.L., Erwin, J.M., Hof, P.R., Sherwood, C.C., 2007. Cholinergic innervation of the frontal cortex: differences among humans, chimpanzees, and macaque monkeys. Journal of Comparative Neurology 506, 409–424.

Raghanti, M.A., Stimpson, C.D., Marcinkiewicz, J.L., Erwin, J.M., Hof, P.R., Sherwood, C.C., 2008a. Cortical dopaminergic innervation among humans, chimpanzees, and macaque monkeys: a comparative study. Neuroscience 155, 203–220.

Raghanti, M.A., Stimpson, C.D., Marcinkiewicz, J.L., Erwin, J.M., Hof, P.R., Sherwood, C.C., 2008b. Differences in cortical serotonergic innervation among humans, chimpanzees, and macaque monkeys: a comparative study. Cerebral Cortex 18, 584–597.

Raghanti, M.A., Spocter, M.A., Stimpson, C.D., Erwin, J.M., Bonar, C.J., Allman, J.M., Hof, P.R., Sherwood, C.C., 2009. Species-specific distributions of tyrosine hydroxylase–immunoreactive neurons in the prefrontal cortex of anthropoid primates. Neuroscience 158, 1551–1559.

Raghanti, M.A., Spocter, M.A., Butti, C., Hof, P.R., Sherwood, C.C., 2010. A comparative perspective on minicolumns and inhibitory GABAergic interneurons in the neocortex. Front. Neuroanat. 3.

Raghanti, M.A., Edler, M.K., Meindl, R.S., Sudduth, J., Bohush, T., Erwin, J.M., Stimpson, C.D., Hof, P.R., Sherwood, C.C., 2014. Humans and great apes share increased neocortical neuropeptide Y innervation compared to other haplorhine primates. Frontiers in Human Neuroscience 8, 101.

Raichle, M.E., MacLeod, A.M., Snyder, A.Z., Powers, W.J., Gusnard, D.A., Shulman, G.L., 2001. A default mode of brain function. Proceedings of the National Academy of Sciences of the United States of America 98, 676–682.

Ramayya, A.G., Ramayya, A.G., Glasser, M.F., Glasser, M.F., Rilling, J.K., Rilling, J.K., 2010. A DTI investigation of neural substrates supporting tool use. Cerebral Cortex 20, 507–516.

Reimers-Kipping, S., Hevers, W., Paabo, S., Enard, W., 2011. Humanized Foxp2 specifically affects cortico-basal ganglia circuits. Neuroscience 175, 75–84.

Rilling, J.K., Insel, T.R., 1999. The primate neocortex in comparative perspective using magnetic resonance imaging. Journal of Human Evolution 37, 191–223.

Rilling, J.K., Stout, D., 2014. Evolution of the neural bases of higher cognitive function in humans. In: Gazzaniga, M.S., Mangun, G. (Eds.), The Cognitive Neurosciences, fifth ed. MIT Press, Cambridge, MA, pp. 41–49.

Rilling, J.K., Barks, S.K., Parr, L.A., Preuss, T.M., Faber, T.L., Pagnoni, G., Bremner, J.D., Votaw, J.R., 2007. A comparison of resting-state brain activity in humans and chimpanzees. Proceedings of the National Academy of Sciences of the United States of America 104, 17146–17151.

Rilling, J.K., Glasser, M.F., Preuss, T.M., Ma, X., Zhao, T., Hu, X., Behrens, T.E.J., 2008. The evolution of the arcuate fasciculus revealed with comparative DTI. Nature Neuroscience 11, 426–428.

Rilling, J.K., Glasser, M.F., Jbabdi, S., Andersson, J., Preuss, T.M., 2011. Continuity, divergence, and the evolution of brain language pathways. Frontiers in Evolutionary Neuroscience 1–6.

Rilling, J.K., 2008. Neuroscientific approaches and applications within anthropology. American Journal of Physical Anthropology (Suppl. 47), 2–32.

Rockel, A.J., Hiorns, R.W., Powell, T.P.S., 1980. The basic uniformity in structure of the neocortex. Brain 103, 221–244.

Rosa, M.G., Tweedale, R., 2005. Brain maps, great and small: lessons from comparative studies of primate visual cortical organization. Philosophical Transactions of the Royal Society B: Biological Sciences 360, 665–691.

Sallet, J., Mars, R.B., Noonan, M.P., Neubert, F.-X., Jbabdi, S., O'Reilly, J.X., Filippini, N., Thomas, A.G., Rushworth, M.F., 2013. The organization of dorsal frontal cortex in humans and macaques. The Journal of Neuroscience 33, 12255–12274.

Schenker, N.M., Buxhoeveden, D.P., Blackmon, W.L., Amunts, K., Zilles, K., Semendeferi, K., 2008. A comparative quantitative analysis of cytoarchitecture and minicolumnar organization in Broca's area in humans and great apes. Journal of Comparative Neurology 510, 117–128.

Schoenemann, P.T., 2006. Evolution of the size and functional areas of the human brain. Annual Review of Anthropology 35, 379–406.

Schoenemann, P.T., 2012. Evolution of brain and language. Progress in Brain Research 195, 443–459.

Seeley, W.W., Merkle, F.T., Gaus, S.E., Craig, A.D., Allman, J.M., Hof, P.R., Economo, C.V., 2012. Distinctive neurons of the anterior cingulate and frontoinsular cortex: a historical perspective. Cerebral Cortex 22, 245–250.

Semendeferi, K., Damasio, H., 2000. The brain and its main anatomical subdivisions in living hominoids using magnetic resonance imaging. Journal of Human Evolution 38, 317–332.

Semendeferi, K., Armstrong, E., Schleicher, A., Zilles, K., Van Hoesen, G.W., 2001. Prefrontal cortex in humans and apes: a comparative study of area 10. American Journal of Physical Anthropology 114, 224–241.

Semendeferi, K., Lu, A., Schenker, N., Damasio, H., 2002. Humans and great apes share a large frontal cortex. Nature Neuroscience 5, 272–276.

Sherwood, C.C., Subiaul, F., Zawidzki, T.W., 2008. A natural history of the human mind: tracing evolutionary changes in brain and cognition. Journal of Anatomy 212, 426–454.

Somel, M., Franz, H., Yan, Z., Lorenc, A., Guo, S., Giger, T., Kelso, J., Nickel, B., Dannemann, M., Bahn, S., Webster, M.J., Weickert, C.S., Lachmann, M., Paabo, S., Khaitovich, P., 2009. Transcriptional neoteny in the human brain. Proceedings of the National Academy of Sciences of the United States of America 106, 5743–5748.

Stout, D., Passingham, R., Frith, C., Apel, J., Chaminade, T., 2011. Technology, expertise and social cognition in human evolution. European Journal of Neuroscience 33, 1328–1338.

Stout, D., 2011. Stone toolmaking and the evolution of human culture and cognition. Philosophical Transactions of the Royal Society B: Biological Sciences 366, 1050–1059.

Teffer, K., Semendeferi, K., 2012. Human prefrontal cortex: evolution, development, and pathology. Progress in Brain Research 195, 191–218.

Tootell, R.B., Mendola, J.D., Hadjikhani, N.K., Ledden, P.J., Liu, A.K., Reppas, J.B., Sereno, M.I., Dale, A.M., 1997. Functional analysis of V3A and related areas in human visual cortex. The Journal of Neuroscience 17, 7060–7078.

Torta, D.M., Cauda, F., 2011. Different functions in the cingulate cortex, a meta-analytic connectivity modeling study. NeuroImage 56, 2157–2172.

Uddin, M., Wildman, D.E., Liu, G., Xu, W., Johnson, R.M., Hof, P.R., Kapatos, G., Grossman, L.I., Goodman, M., 2004. Sister grouping of chimpanzees and humans as revealed by genome-wide phylogenetic analysis of brain gene expression profiles. Proceedings of the National Academy of Sciences of the United States of America 101, 2957–2962.

van den Heuvel, M.P., Sporns, O., 2013. Network hubs in the human brain. Trends in Cognitive Sciences (Regul. Ed.) 17, 683–696.

Van Essen, D.C., Lewis, J.W., Drury, H.A., Hadjikhani, N., Tootell, R.B., Bakircioglu, M., Miller, M.I., 2001. Mapping visual cortex in monkeys and humans using surface-based atlases. Vision Research 41, 1359–1378.

Van Essen, D.C., Smith, S.M., Barch, D.M., Behrens, T.E., Yacoub, E., Ugurbil, K., Consortium, W.U.-M.H, 2013. The WU-Minn human connectome project: an overview. NeuroImage 80, 62–79.

Vanduffel, W., Fize, D., Mandeville, J.B., Nelissen, K., Van Hecke, P., Rosen, B.R., Tootell, R.B., Orban, G.A., 2001. Visual motion processing investigated using contrast agent-enhanced fMRI in awake behaving monkeys. Neuron 32, 565–577.

Vanduffel, W., Fize, D., Peuskens, H., Denys, K., Sunaert, S., Todd, J.T., Orban, G.A., 2002. Extracting 3D from motion: differences in human and monkey intraparietal cortex. Science 298, 413–415.

Vanduffel, W., Zhu, Q., Orban, G.A., 2014. Monkey cortex through fMRI glasses. Neuron 83, 533–550.

Vargha-Khadem, F., Watkins, K., Alcock, K., Fletcher, P., Passingham, R., 1995. Praxic and nonverbal cognitive deficits in a large family with a genetically transmitted speech and language disorder. Proceedings of the National Academy of Sciences of the United States of America 92, 930–933.

Varki, A., Geschwind, D.H., Eichler, E.E., 2008. Explaining human uniqueness: genome interactions with environment, behaviour and culture. Nature Reviews Genetics 9, 749–763.

Vincent, J.L., Patel, G.H., Fox, M.D., Snyder, A.Z., Baker, J.T., Van Essen, D.C., Zempel, J.M., Snyder, L.H., Corbetta, M., Raichle, M.E., 2007. Intrinsic functional architecture in the anaesthetized monkey brain. Nature 447, 83–86.

Vogt, B.A., Hof, P.R., Zilles, K., Vogt, L.J., Herold, C., Palomero-Gallagher, N., 2013. Cingulate area 32 homologies in mouse, rat, macaque and human: cytoarchitecture and receptor architecture. Journal of Comparative Neurology 521, 4189–4204.

Vogt, B.A., 2005. Pain and emotion interactions in subregions of the cingulate gyrus. Nature Reviews 6, 533–544.

Whiten, A., McGuigan, N., Marshall-Pescini, S., Hopper, L.M., 2009. Emulation, imitation, over-imitation and the scope of culture for child and chimpanzee. Philosophical Transactions of the Royal Society B: Biological Sciences 364, 2417–2428.

Wood, B., Baker, J., 2011. Evolution in the genus *Homo*. Annual Review of Ecology, Evolution, and Systematics 42, 47–69.

Yeo, B.T., Krienen, F.M., Sepulcre, J., Sabuncu, M.R., Lashkari, D., Hollinshead, M., Roffman, J.L., Smoller, J.W., Zollei, L., Polimeni, J.R., Fischl, B., Liu, H., Buckner, R.L., 2011. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. Journal of Neurophysiology 106, 1125–1165.

Zahn, R., Moll, J., Krueger, F., Huey, E.D., Garrido, G., Grafman, J., 2007. Social concepts are represented in the superior anterior temporal cortex. Proceedings of the National Academy of Sciences of the United States of America 104, 6430–6435.

Chapter 9

How Different Are Humans and "Great Apes"? A Matrix of Comparative Anthropogeny

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THE CHALLENGE OF COMPARATIVE ANTHROPOGENY

Comparisons of nonhuman hominids with humans are difficult, as so little is known about their phenotypic features (great ape phenomes), in contrast to what we know about humans (Varki et al., 1998). Ethical, fiscal, and practical issues also limit collection of further data about these species (Gagneux et al., 2005; McConkey and Varki, 2005), all of which are currently endangered in the wild. A Matrix of Comparative Anthropogeny (MOCA) has been established at the website of the Center for Academic Research and Training in Anthropogeny (CARTA), and attempts to collect existing information about human-specific differences from "great apes" currently scattered in the literature. Having such information in one location could lead to new insights and multidisciplinary interactions, and to ethically sound studies to explain differences and uniquely human specializations. It is for this reason that MOCA is called a matrix, ie, an arrangement of information from which something else originates, develops, or takes form. This approach could allow us to connect the dots between different human specializations, and shed light on how and in what sequence each difference came about.

OUR EVOLUTIONARY HERITAGE AND PRIMATE NATURE

Classification

Humans are one of approximately 400 primate species. Eighty million years of evolution have given rise to a staggering range of primate species, ranging in size like that of a small rodent, to the several 100 pound gorilla silverbacks (Martin, 2012). The fossil record places human origins firmly in Africa, with ~4 million years of bipedal hominin evolution on that continent before the first hominin fossils appear outside Africa (Antón et al., 2014). Following initial waves of migration of members of the genus *Homo* out of Africa, there was a final migration of behaviorally modern *Homo sapiens* from Africa, a species that replaced all other extant members of the hominin clade, with limited interbreeding (Varki, 2013; Pääbo, 2015).

Common Phenotypic Features of Humans

Like most other primates, humans are usually born as singletons, have long lactation periods, and manifest a relatively slow development of the young. Like most nonhuman hominids, humans are also long-lived, and belong to complex social groups. Humans have the same number of bones and teeth as chimpanzees (with the exception of a missing baculum/penis bone in human males). Similarities in the organization of our brains are also obvious, such as the sharing of all major areas and a six-layered cortex. It is not uncommon for a human observer of wild chimpanzees to be reminded of human acquaintances through one of the ape subjects. But these individuals have and use no names, never sit around a fire, and they do not discuss the details of yesterday or plan for tomorrow.

Comparative Genomics

Our genomes have a very similar size (~3 billion base pairs for each parental haploid genome) to those of our closest relatives and even show similar packaging into

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00009-0

chromosomes (with the exception of a fused chromosome in humans, we have 23 pairs as compared to the 24 pairs found in great apes; Ventura et al., 2012). The total number of genes is also similar. Complete sequencing of the great ape genomes confirmed that these are very similar to our own (Prado-Martinez et al., 2013). At the level of alignable sequences we are ~99% identical. However, around 5% of the total DNA in the chimpanzee genome differs from that of humans, if one considers the DNA that is missing in either species but present in the other (Britten, 2002). With the discovery of novel functional elements in our genomes comes the realization that noncoding DNA differences probably play important roles in the regulation of gene expression (Capra et al., 2013). This supports the classical suggestion that regulatory changes likely explain much of the phenotypic differences between humans and our ape relatives (King and Wilson, 1975).

COMPARATIVE ANTHROPOGENY

What Is Anthropogeny?

Anthropogeny is a classic term encompassing the exploration of the origins of the human species (Hooper, 1839). It contrasts with traditional anthropology, which includes the much broader study of modern humans and their varied cultures and behaviors, as well as studies of other primates.

A Comprehensive Comparative Approach Is Needed

Given the lack of understanding of the factors that shaped the evolution of our species from ape-like ancestors over the last 6 million years or so, explaining the origin of the human phenomenon will critically rely on interactive insights gained from drastically different scientific domains: biological, social, medical, physical, and computational (see Fig. 9.1).

Limited Information Is Available on the Phenomes of Nonhuman Hominids

Compared with the vast store of information we have on humans, our knowledge of great ape phenomes is very limited (Fig. 9.2). All living great ape species are currently also endangered due to the rapid destruction or deterioration of their habitats (tropical forests in Africa and Southeast Asia), predation by human bush meat hunting, and emerging infectious diseases arising from ecological disturbances. In the best of all possible worlds there would be a concerted effort to more fully understand the phenomes of their captive counterparts, not only for the purposes of understanding human origins, but also for improving the care for these endangered populations (Gagneux et al., 2005). However, traditionally, only chimpanzees have been kept for research purposes, with very few

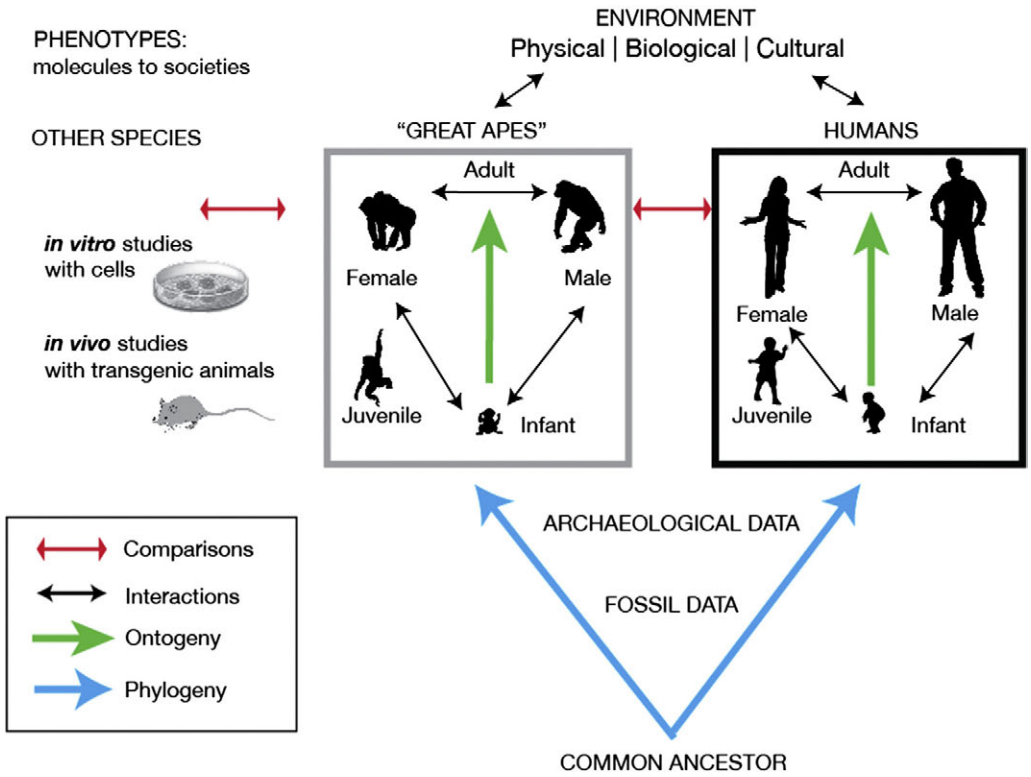

FIGURE 9.1 A systematic approach to Anthropogeny. *Updated by P. Gagneux, from Varki, A., Nelson, D., 2007. Genomic differences between humans and chimpanzees. Annual Review of Anthropology 36, 191–209.*

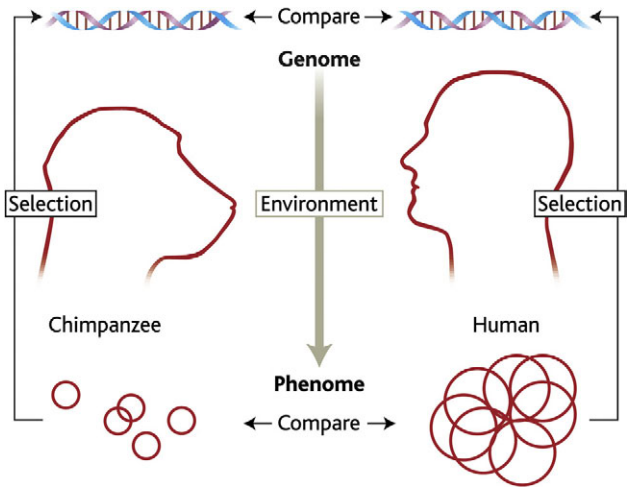

FIGURE 9.2 The need for more information about "great ape" phenomes. *Reproduced from McConkey, E.H., Varki, A., 2005. Genomics. Thoughts on the future of great ape research. Science 309, 1499–1501.*

bonobos, gorillas, or orangutans in captivity (mostly restricted to zoos). Research activities on captive great apes have also now all but ceased around the world with few notable exceptions: Japan, the United States, Gabon, and African ape sanctuaries. There are several dozen great ape research sites where great apes are studied in their natural environment, and most of these sites have ape populations that are completely habituated to the presence of human observers. These provide precious remaining research opportunities but unfortunately, also greatly increase the risk of predation and infectious disease to these populations (Kondgen et al., 2008).

Ethical and Practical Limitations on Further Acquisition of Information

The phylogenetic proximity and psychological similarity of great apes and humans have raised strong objections and prompted legislation prohibiting any invasive or destructive research on these species (Altevogt et al., 2011; de Waal, 2012). However, routine medical care of captive populations remaining in sanctuaries could generate urgently needed materials to enhance our knowledge of great ape basic biology (Gagneux et al., 2005). In practice, opportunities to collect more phenotypic information on these species remains limited, and the current situation of asymmetric phenotypic information is unlikely to ever change for the better.

Body, Mind, and Society of Humans Show Major Departures From Those of "Great Apes"

Humans differ from great ape species in external and internal anatomy, cognition, and social behavior in many important ways. This, and a good dose of anthropocentrism, explain why our closest relatives the chimpanzees were traditionally grouped into the nonexistent taxonomic group that used to be called "pongids" or colloquially, the "great apes." A systematic approach to human differences from these close evolutionary cousins is exemplified by MOCA.

MATRIX OF COMPARATIVE ANTHROPOGENY

Origins and Rationale

MOCA started as a simple list of features allegedly unique to humans kept by one of us (A.V.). With the establishment of CARTA came the opportunity to expand and correct this list, which has grown into over 500 items (topics) falling into 24 different domains (see section: Organization Into Domains of Human Knowledge in this chapter).

Goals

MOCA attempts to collect existing information currently scattered in the literature about human-specific differences from great apes (O'Bleness et al., 2012). Having such information in one location could lead to new insights and multidisciplinary interactions, and to ethically sound studies to explain differences, as well as uniquely human specializations. This is why MOCA is called a matrix. This approach will hopefully allow us to connect the dots among different human specializations and shed light on how and in what sequence these have evolved. Furthermore, it may allow us to connect different specializations and potentially discover which ones may have caused others. Importantly, such a chronology will be very helpful in ruling out certain scenarios due to inconsistencies in timing. By definition, MOCA will always be a work in progress.

Organization Into Domains of Human Knowledge

MOCA is organized into 24 different alphabetically sorted domains based on areas of scientific knowledge, and each topic is assigned to the domain it most closely relates to. Topics are cross-listed with other topics across all domains whenever warranted. For example the entry on "composition of milk" in the MOCA domain Biochemistry would be cross-listed with blood group antigens (Pathology), domestication (Behavior), duration of lactation (Development), parental investment (General Life History), sialic acid content of the brain (Neuroscience), difficulty in breastfeeding, and breast development without pregnancy/lactation (Reproductive Biology and Disease), and should further be cross-listed with microbiome (Ecology).

SELECTED EXAMPLES OF COMPARATIVE ANTHROPOGENY

Space does not allow a systematic and complete summary of the information currently in the MOCA resource. The following is a brief mention of just a few topics in each of the 24 domains.

Anatomy and Biomechanics

Among the striking human features are reduced fur, upright posture and ability for sustained running (Bramble and Lieberman, 2004), visible sclera (whites) of the eyes (Tomasello et al., 2007), and a larger and better opposable thumb (Tocheri et al., 2008). Great apes also appear to have much stronger skeletal muscles (Walker, 2009).

Behavior

Humans are an "invasive species" that occupy a wide range of habitats. Some other primate species use a fixed place as night shelter (eg, baboons). Humans build camps or villages and use sites (home bases) for prolonged periods of time. Places, individuals, and social groups have names. The use of fire allowed the transformation of materials (silcrete, pitch, compound adhesives), which opened numerous new possibilities uniquely to our species (Wadley et al., 2009). Cooking with fire profoundly affected the hominin lineage, by allowing access to much wider variety of food sources: plant tubers and seeds could be detoxified, and meat and plants rendered much more easily digestible (Wrangham et al., 1999). Fire also allowed an extension of human daily activity into the night (Wiessner, 2014) and the colonization of much colder ecosystems (Roebroeks and Villa, 2011). The use of fire and other controlled energy sources eventually launched the anthropocene, an epoch in which humans have been altering landscapes, climate, and the fate of countless animal species (Balter, 2013).

Cell Biology and Chemistry

The composition of milk is different between humans and other hominids. Like humans, great apes produce milk with a much higher number of free milk oligosaccharides than most mammals do (over 200 compared to 50) (Urashima et al., 2009). But humans appear to have longer oligosaccharides and lack the ability to produce the sialic acid Neu5Gc in their milk (and in the rest of their body) (Tao et al., 2011).

Cognition

Drastic differences in cognitive development include very early tendencies of shared attention in humans and rapid language acquisition by normal children learning thousands of words by age three and often multiple languages. Human children exhibit profound interest in others' minds and pronounced prosocial tendencies (Jaeggi et al., 2010). Social cognition also develops earlier in human children (Wobber et al., 2014), and could be related to cooperative breeding in our species (Hrdy, 2009).

Communication

Perhaps one of the most important human characteristics is our linguistic capacity. Whereas other primates clearly communicate, their communication system is not open-ended, ie, they do not have means to convey infinite meanings and information about events displaced in time and space (ie, displaced reference) (Penn et al., 2008). Symbols open up possibilities of defining identity and practicing magic. Language also allows sharing of minds by communication about events and concepts removed in time and space. Importantly, language also allows for gauging individual reputation, the existence of which profoundly affects the likelihood of altruistic acts, even when these are not mutualistic (Fehr, 2004). The origin of human language remains a very contested field of research. The role of gesture and music as launching systems for spoken language are worth investigating (Fay et al., 2014) and so are tantalizing connections between complex (Acheulian and Levallois) stone tool manufacture and the need and capacity for syntax (Stout and Chaminade, 2007; Stout et al., 2015).

Culture

The effective intergenerational transmission of information with language and theory of mind allows for rapid ratcheting of cultural innovations even across societies (Tennie et al., 2009). Such networks made possible trade of rare materials such as shells, pigments, and obsidian. All large human societies have institutions, which are involved in regulating the lives and interactions of society members. Such institutions can also contribute to high levels of social stress, as those individuals with the power to control the institutions can strongly interfere with the lives of large numbers of individuals in their societies. Key biological phenomena regulated by cultures include sexual and reproductive behaviors (Pemberton et al., 2012).

Dental Biology and Disease

Humans lack a pronounced sexual dimorphism in their canines (Plavcan, 2012). The much shortened face and jaw of humans contributes to the impaction of wisdom teeth. While humans and their hominin ancestors also have much thicker enamel than extant apes (Horvath et al., 2014), the overall size of human molars is much reduced, possibly due

to the long history of consuming cooked food and much reduced need for chewing (Wrangham et al., 1999).

Development

Human development, especially neurodevelopment is delayed even further, far beyond that seen in other primates. A high fetal rate of brain growth is maintained throughout gestation and continues in the first year of life (Leigh, 2004). Myelination (the insulation of nerve fibers) in humans is only complete in the third decade—in contrast to chimpanzees, where the process completes around age 10 (Miller et al., 2012).

Ecology

Humans occupy the highest trophic level in most environments. The use of technology such as fire, projectile weapons, hunting machines (nets, traps, snares), and animals skins for warmth and protection has allowed humans to colonize ecosystems around the world. Our species has also increasingly engaged in niche construction (Rendell et al., 2011; Creanza and Feldman, 2014). The ability to swim and to manufacture watercraft (rafts, floats, and boats) further supported the spread of our species.

Endocrinology

Chimpanzees may have higher levels of active thyroid hormone in their circulation (Gagneux et al., 2001). Evidence suggests potential changes in dehydroepiandrosterone (DHEA) metabolism (Blevins et al., 2013) and a unique adolescent growth spurt (Bogin, 1999), potentially mediated by hormones.

General Life History

Childhood, defined as a relative slowing in somatic growth but continued brain development, and the postreproductive survival of females appear to be uniquely human, among primates. Both phenomena contribute to the transfer of behavior, language, and culture between generations (Bogin, 2009) and are linked to the cooperative nature of human child rearing (Hrdy, 2009).

Genetics

While the vast majority of genes are shared between humans and other hominids, there are a few that only exist functionally in humans or in chimpanzees (O'Bleness et al., 2012). Many regulatory regions in the genome have also undergone changes unique to humans or to one of the other ape (hominid) lineages. Examples abound. Multiple changes have occurred in genes associated with sialic acid biology (Varki, 2010). Human accelerated regions have been identified and include DNA coding for small regulatory RNA (Capra et al., 2013). Several of these functional genomic elements affect brain cortical development in utero (McLean et al., 2011; Charrier et al., 2012; Boyd et al., 2015; Reilly et al., 2015). Studies of gene expression patterns in a variety of tissues and individuals of varying ages are rapidly adding formidable amounts of data with high relevance for understanding human specific phenotypes, eg, brain gene expression, testes gene expression (Khaitovich et al., 2006; Somel et al., 2009).

Genomics

The levels of genetic diversity tend to be surprisingly high in most great ape populations, which despite their low numbers, maintain over twice the diversity found in humans. Notable exceptions are bonobo and mountain gorillas, which exhibit levels of genetic diversity lower than humans (Prado-Martinez et al., 2013). Unstable repeat elements in the genome of great apes have differentially expanded in chimpanzees and gorillas (Marques-Bonet et al., 2009). Recent families of transposable elements and endogenous retroviruses have differentially expanded and inserted in humans and chimpanzees (Magiorkinis et al., 2015). Most recently, evidence for differential and strong selection on the X chromosomes of great apes has been interpreted as resulting from lineage specific control of selfish (testis expressed, meiotic drive) elements on large tracts of the X chromosome (Nam et al., 2015).

Immunology

Several aspects of the human immune system have recently been modified by natural selection, possibly due to the unique pathogen regimes that humans encountered. Possibly related to this, humans have undergone biochemical changes with regard to certain molecules found on the surface of most of their cells as well as receptors on a variety of immune cells (Parham et al., 2012; Varki, 2010). Much research is currently focused on understanding how the microbiome of humans and their closest living relatives contributes to immune system maturation, and how humans came to carry much reduced microbial diversity (Moeller et al., 2014).

Medical Diseases

There are many differences in disease susceptibility between humans and other hominids. Examples include *falciparum* Malaria, Influenza A, frequency of progression of HIV infection to AIDS, and bacterial sexually transmitted infections (*chlamydia*, chancroid, syphilis, and gonorrhea) (Varki and Varki, 2015; Varki et al., 2011).

Mental Disease

Humans are prone to a range of mental diseases never so far diagnosed in any ape. These include early onset syndromes such as autism, but also later onset diseases such as bipolar disorder, schizophrenia, and Alzheimer's disease.

Neuroscience

Relative to body size, the human brain is three times larger than any ape brain. However some of the early claims of major regional allometric differences between human and other primate brains have not been substantiated (Semendeferi et al., 1997). But much new evidence has been found for differences in cellular architecture, the packing of mini columns in several cortical areas (Schenker et al., 2008), as well as in connectivity, such as the massively increased arcuate fasciculus connecting language areas in humans (Rilling et al., 2008). Comparing gene expression in different brain regions across species also revealed that micro RNAs are involved in shaping human-specific brain development (Somel et al., 2011). The emerging field of stem cell and induced pluripotent cell biology allows direct comparison of human and nonhominid cells in vitro. Derived neuronal cell lineages exhibit interesting differences in gene expression, motility, and branching patterns (Marchetto et al., 2013).

Nutrition

Hominin ancestors used their technical and cognitive skills to become top predators around 2 million years ago. While some great apes regularly hunt and consume a range of vertebrate prey, only humans habitually hunt and sometimes even cover much of their caloric intake with meat (at higher latitudes). The use of fire brought with it the invention of cooking. Cooking allows access to novel food as it detoxifies tubers and seeds, renders food much more digestible and easy to chew, and also permits the preserving of animal foods by smoking (Smith et al., 2015).

Organ Physiology

Heat dissipation through eccrine sweating, and the phenomenon of emotional lacrimation (crying) appear unusually pronounced in humans. Emotional blushing is a physiological reaction to social embarrassment and has never been described in nonhumans, and one of the most peculiar emotions of humans (Darwin, 1872). The reaction occurs in all humans but is more readily visible in individuals with light (melanin poor) skin.

Pathology

Cancers of epithelial origin (carcinomas) appear to be rare in nonhuman hominids but are among the most common killers in our species (Varki and Varki, 2015). Also not been described in the great apes is Alzheimer's disease (Finch and Austad, 2014) or coronary thrombosis (Varki et al., 2009).

Pharmacology

Most human societies use mind-altering drugs. There are no reports of wild apes using such agents, even though wild chimpanzees have been shown to self-medicate by ingesting plants (Huffman, 2003). Psychedelic drugs can contain psychoactive chemicals that induce altered states of consciousness, including spiritual sensations (Sullivan and Hagen, 2002).

Reproductive Biology and Disease

While pair-bonding is very common in human societies, none of the other primates exhibit prolonged pair-bonding in the context of multimale, multifemale groups. A certain degree of confidence in paternity combined with personal names and kinship terms allows for paternal kinship networks spanning many social groups, allowing for the existence of clans and tribes (Chapais, 2013). The prolonged postreproductive survival of females allows grandmothers to help with the care of the young, and also to pass on much cultural information (Kim et al., 2014). Cultural transmission by the elderly might even have allowed selection for genetic variants that protect cognitive capacities late in life (Schwarz et al., 2015; Hawkes, 2015). Cooperative breeding is also strongly distinctive of humans, as compared to all the great apes (Hrdy, 2009).

Skin Biology and Disease

Reduced hair, increased subcutaneous fat, and a great variation in skin, hair, and eye pigmentation are unusual human features (Jablonski, 2012; Kuzawa, 1998). Permanent breast development in adult human females is another obvious difference (Dixson, 2009).

Social Organization

For most of human prehistory, preagricultural humans lived in small groups but large social networks. Larger groups, even larger social networks, and complex hierarchies, arose among agrarian societies (Smail, 2008).

TOPIC TIMELINES AND RELATIONSHIPS

How are these and other uniquely human features functionally related to each other and which ones arose first along the lineage leading to humans? As an example, a rough sequence of major items based on current evidence would be as follows: facultative bipedality, changes in the hand anatomy, full striding/running bipedality, control of fire, cooking, home base use, much larger brains, burials,

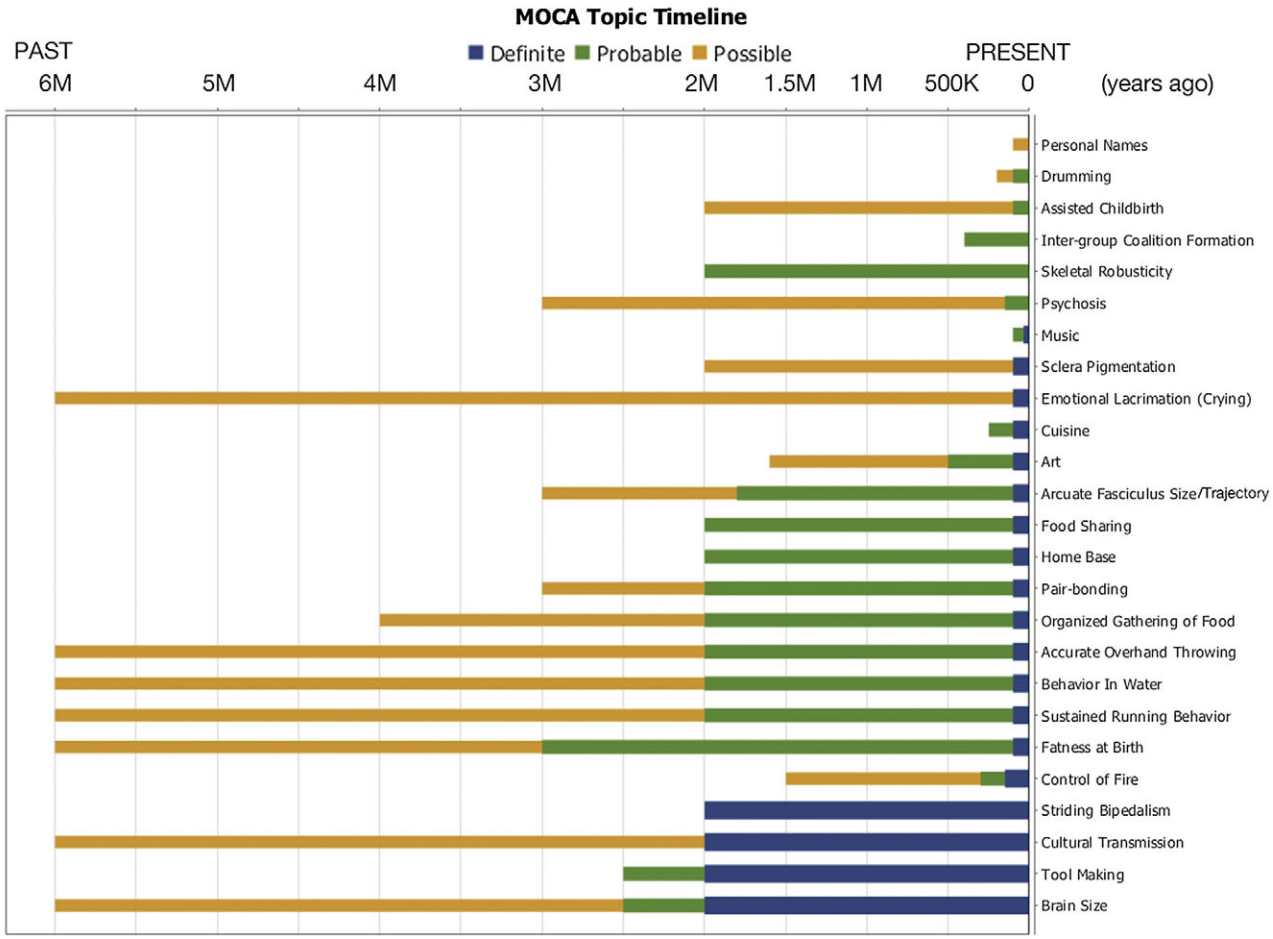

FIGURE 9.3 Example of timeline analysis derived from Matrix of Comparative Anthropogeny (MOCA) topic data.

symbolic capacity, and projectile weapons. There is a special problem with obtaining definitive time lines for various forms of cognitive behavior such as musicality and language, which do not easily leave fossil evidence. This is also true of more ephemeral materials like ropes and nets. But with most apparently human-unique features it is possible to assign three rough time points at which the emergence of the feature may have occurred: possible, probable, and definite. Shown in Fig. 9.3 is an example of a collection of such timelines for various prominent examples of uniquely human features, relative to the great apes. Someday, if such a diagram could contain definitive dating for the emergence of all of the items in MOCA, the story of human origins would essentially tell itself.

GENERATING NETWORKS OF RELATIONSHIPS AMONG MATRIX OF COMPARATIVE ANTHROPOGENY TOPICS

Volunteer writers of MOCA topic entries are encouraged to indicate relationships to other topics, designated at the same three levels as above: possible, probable, and definitive. As such entries are completed it will be increasingly feasible to create complex networks of relationships between many uniquely human features. An early example of such a network is shown in Fig. 9.4. Connections arising from genetic and genomic topic entries will eventually emerge, bringing together the roles of nature and nurture in the origin and evolution of our species.

SYNTHESIS WITH EXISTING THEORIES OF HUMAN ORIGINS

There is no shortage of so-called "umbrella hypotheses," which try to explain most, if not all, human features based on one underlying mechanism. Given the long time period during which hominins evolved from one or possibly a combination of some ancestral lineages giving rise to modern humans, this is extremely unlikely. On the other hand each of the theories may have something to contribute to understanding human origins. They can all now be reexamined in the context of MOCA Topics, Timelines, and Networks. Eventually, new theories and syntheses may emerge.

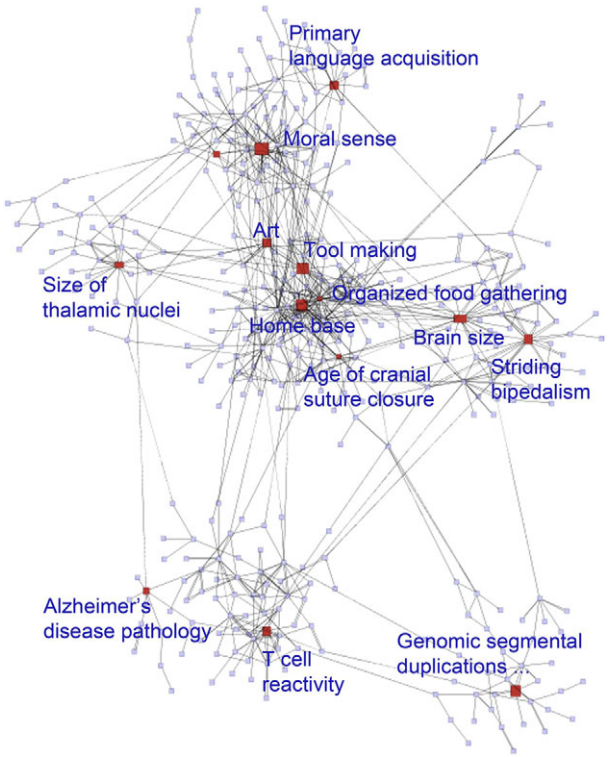

FIGURE 9.4 Example of a relational Matrix of Comparative Anthropogeny (MOCA) topics.

CAVEAT: ABSENCE OF EVIDENCE IN NONHUMAN PRIMATES IS NOT EVIDENCE FOR ABSENCE

Many aspects of claimed human uniqueness have been challenged in recent times. For example, symbolic communication is well documented in several species of nonhuman primates (vervets, guenons). Cultural phenomena have been well described in common chimpanzees, where different types of complex tool uses and foraging behaviors are clearly passed on intergenerationally, by observational learning (Tennie et al., 2009). By the same token, there is no evidence that chimpanzees are aware (have a meta-representation) of their own cultures (Gruber et al., 2015).

MOVING THE GOALPOSTS

With each discovery of a human-like behavior in a nonhuman primate, there is a tendency to redefine the human-like trait so as to exclude the new observation. One is then accused of "moving the goalposts" each time this happens. The problem may lie with where the goalposts were placed to begin with. We should be comparing the capabilities of the average adult human with that of the average great ape, not that of the most successful ape known with that of a four-year-old human. But then, one might be accused of being anthropocentric and promoting human exceptionalism. While there are indeed many risks involved in pursuing such views, a balanced approach to anthropogeny inherently requires an emphasis on human uniqueness.

CONCLUSIONS AND FUTURE PROSPECTS

It is abundantly clear that the long list of attributes setting humans apart from their ape relatives did not arise overnight, nor were they driven by a single factor. Rather, these traits are the combinatorial outcome of over 6 million years of evolution, during which ancestral populations experienced successive and potentially conflicting selective pressures arising from climate, competition with other species, infectious disease, demographic collapse and recovery, founder events (bottle necks), and niche construction, whereby our ancestors set in place ecological and social-cultural niches which in turn exerted strong selection on past populations. While it is very informative to ponder the circumstances that could have exerted these combined effects on our species, the lack of any other species with symbolic, linguistic, and ratcheting culture makes for an immense challenge when attempting an evidence-based approach to anthropogeny. Humans are both "biologically cultural" with brain development requiring linguistic input and "culturally biological" as cultural practices such as cooking actively changed human biology. The evident animal nature of humans combined with these many human-unique attributes make for a striking paradox.

REFERENCES

Altevogt, B.M., Pankevich, D.E., Shelton-Davenport, M.K., Kahn, J.P., 2011. Chimpanzees in Biomedical and Behavioral Research: Assessing the Necessity. Washington, DC.

Antón, S.C., Potts, R., Aiello, L.C., 2014. Human evolution. Evolution of early *Homo*: an integrated biological perspective. Science 345, 1236828.

Balter, M., 2013. Archaeology. Archaeologists say the 'Anthropocene' is here—but it began long ago. Science 340, 261—262.

Blevins, J.K., Coxworth, J.E., Herndon, J.G., Hawkes, K., 2013. Brief communication: adrenal androgens and aging: female chimpanzees (*Pan troglodytes*) compared with women. American Journal of Physical Anthropology 151, 643—648.

Bogin, B., 1999. Evolutionary perspective on human growth. Annual Review of Anthropology 28, 109—153.

Bogin, B., 2009. Childhood, adolescence, and longevity: a multilevel model of the evolution of reserve capacity in human life history. American Journal of Human Biology 21, 567—577.

Boyd, J.L., Skove, S.L., Rouanet, J.P., et al., 2015. Human-chimpanzee differences in a FZD8 enhancer alter cell-cycle dynamics in the developing neocortex. Current Biology 25, 772—779.

Bramble, D.M., Lieberman, D.E., 2004. Endurance running and the evolution of *Homo*. Nature 432, 345—352.

Britten, R.J., 2002. Divergence between samples of chimpanzee and human DNA sequences is 5%, counting indels. Proceedings of the National Academy of Sciences of the United States of America 99, 13633—13635.

Capra, J.A., Erwin, G.D., McKinsey, G., Rubenstein, J.L., Pollard, K.S., 2013. Many human accelerated regions are developmental enhancers. Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences 368, 20130025.

Chapais, B., 2013. Monogamy, strongly bonded groups, and the evolution of human social structure. Evolutionary Anthropology 22, 52–65.

Charrier, C., Joshi, K., Coutinho-Budd, J., et al., 2012. Inhibition of SRGAP2 function by its human-specific paralogs induces neoteny during spine maturation. Cell 149, 923–935.

Creanza, N., Feldman, M.W., 2014. Complexity in models of cultural niche construction with selection and homophily. Proceedings of the National Academy of Sciences of the United States of America 111 (Suppl. 3), 10830–10837.

Darwin, C., 1872. The Expression of the Emotions in Man and Animals. J. Murray, London.

de Waal, F.B., 2012. Research chimpanzees may get a break. PLoS Biology 10, e1001291.

Dixson, A.F., 2009. Sexual Selection and the Origins of Human Mating Systems. Oxford University Press, Oxford; New York.

Fay, N., Lister, C.J., Ellison, T.M., Goldin-Meadow, S., 2014. Creating a communication system from scratch: gesture beats vocalization hands down. Frontiers in Psychology 5, 354.

Fehr, E., 2004. Human behaviour: don't lose your reputation. Nature 432, 449–450.

Finch, C.E., Austad, S.N., 2014. Commentary: is Alzheimer's disease uniquely human? Neurobiology of Aging 36 (2), 553–555.

Gagneux, P., Amess, B., Diaz, S., et al., 2001. Proteomic comparison of human and great ape blood plasma reveals conserved glycosylation and differences in thyroid hormone metabolism. American Journal of Physical Anthropology 115, 99–109.

Gagneux, P., Moore, J.J., Varki, A., 2005. The ethics of research on great apes. Nature 437, 27–29.

Gruber, T., Zuberbühler, K., Clément, F., van Schaik, C., 2015. Apes have culture but may not know that they do. Frontiers in Psychology 6, 91.

Hawkes, K., 2015. Genomic evidence for the evolution of human post-menopausal longevity. Proceedings of the National Academy of Sciences of the United States of America 113 (1), 17–18.

Hooper, R., 1839. A New Medical Dictionary Containing the Explanation of the Terms in Anatomy, Chemistry, Physiology, Pharmacy, Practice of Physic, Surgery, Materia Medica, Midwifery, and the Various Branches of Natural Philosophy Connected With Medicine. M. Carey & Son, Benjamin Warner, and Edward Parker. Griggs & Company Printers, Philadelphia.

Horvath, J.E., Ramachandran, G.L., Fedrigo, O., et al., 2014. Genetic comparisons yield insight into the evolution of enamel thickness during human evolution. Journal of Human Evolution 73, 75–87.

Hrdy, S.B., 2009. Mothers and Others: The Evolutionary Origins of Mutual Understanding. Belknap Press of Harvard University Press, Cambridge, MA.

Huffman, M.A., 2003. Animal self-medication and ethno-medicine: exploration and exploitation of the medicinal properties of plants. Proceedings of the Nutrition Society 62, 371–381.

Jablonski, N.G., 2012. Human skin pigmentation as an example of adaptive evolution. Proceedings of the American Philosophical Society 156, 45–57.

Jaeggi, A.V., Burkart, J.M., Van Schaik, C.P., 2010. On the psychology of cooperation in humans and other primates: combining the natural history and experimental evidence of prosociality. Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences 365, 2723–2735.

Khaitovich, P., Enard, W., Lachmann, M., Paabo, S., 2006. Evolution of primate gene expression. Nature Reviews Genetics 7, 693–702.

Kim, P.S., McQueen, J.S., Coxworth, J.E., Hawkes, K., 2014. Grandmothering drives the evolution of longevity in a probabilistic model. Journal of Theoretical Biology 353, 84–94.

King, M.C., Wilson, A.C., 1975. Evolution at two levels in humans and chimpanzees. Science 188, 107–116.

Kondgen, S., Kuhl, H., N'Goran, P.K., et al., 2008. Pandemic human viruses cause decline of endangered great apes. Current Biology 18, 260–264.

Kuzawa, C.W., 1998. Adipose tissue in human infancy and childhood: an evolutionary perspective. American Journal of Physical Anthropology (Suppl. 27), 177–209.

Leigh, S.R., 2004. Brain growth, life history, and cognition in primate and human evolution. American Journal of Primatology 62, 139–164.

Magiorkinis, G., Blanco-Melo, D., Belshaw, R., 2015. The decline of human endogenous retroviruses: extinction and survival. Retrovirology 12, 8.

Marchetto, M.C., Narvaiza, I., Denli, A.M., et al., 2013. Differential L1 regulation in pluripotent stem cells of humans and apes. Nature 503, 525–529.

Marques-Bonet, T., Kidd, J.M., Ventura, M., et al., 2009. A burst of segmental duplications in the genome of the African great ape ancestor. Nature 457, 877–881.

Martin, R.D., 2012. Primates. Current Biology 22, R785–R790.

McConkey, E.H., Varki, A., 2005. Genomics. Thoughts on the future of great ape research. Science 309, 1499–1501.

McLean, C.Y., Reno, P.L., Pollen, A., et al., 2011. Human-specific loss of regulatory DNA and the evolution of human-specific traits. Nature 471, 216–219.

Miller, D.J., Duka, T., Stimpson, C.D., et al., 2012. Prolonged myelination in human neocortical evolution. Proceedings of the National Academy of Sciences of the United States of America 109, 16480–16485.

Moeller, A.H., Li, Y., Mpoudi Ngole, E., Ahuka-Mundeke, S., et al., 2014. Rapid changes in the gut microbiome during human evolution. Proceedings of the National Academy of Sciences of the United States of America 111, 16431–16435.

Nam, K., Munch, K., Hobolth, A., et al., 2015. Extreme selective sweeps independently targeted the X chromosomes of the great apes. Proceedings of the National Academy of Sciences of the United States of America 112, 6413–6418.

O'Bleness, M., Searles, V.B., Varki, A., Gagneux, P., Sikela, J.M., 2012. Evolution of genetic and genomic features unique to the human lineage. Nature Reviews Genetics 13, 853–866.

Pääbo, S., 2015. The diverse origins of the human gene pool. Nature Reviews Genetics 16, 313–314.

Parham, P., Norman, P.J., Abi-Rached, L., Guethlein, L.A., 2012. Human-specific evolution of killer cell immunoglobulin-like receptor recognition of major histocompatibility complex class I molecules. Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences 367, 800–811.

Pemberton, T.J., Absher, D., Feldman, M.W., Myers, R.M., Rosenberg, N.A., Li, J.Z., 2012. Genomic patterns of homozygosity in worldwide human populations. American Journal of Human Genetics 91, 275–292.

Penn, D.C., Holyoak, K.J., Povinelli, D.J., 2008. Darwin's mistake: explaining the discontinuity between human and nonhuman minds. Behavioral and Brain Sciences 31, 109–130 discussion 130.

Plavcan, J.M., 2012. Sexual size dimorphism, canine dimorphism, and male-male competition in primates: where do humans fit in? Human Nature 23, 45–67.

Prado-Martinez, J., Sudmant, P.H., Kidd, J.M., et al., 2013. Great ape genetic diversity and population history. Nature 499, 471–475.

Reilly, S.K., Yin, J., Ayoub, A.E., et al., 2015. Evolutionary genomics. Evolutionary changes in promoter and enhancer activity during human corticogenesis. Science 347, 1155–1159.

Rendell, L., Fogarty, L., Laland, K.N., 2011. Runaway cultural niche construction. Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences 366, 823–835.

Rilling, J.K., Glasser, M.F., Preuss, T.M., et al., 2008. The evolution of the arcuate fasciculus revealed with comparative DTI. Nature Neuroscience 11, 426–428.

Roebroeks, W., Villa, P., 2011. On the earliest evidence for habitual use of fire in Europe. Proceedings of the National Academy of Sciences of the United States of America 108, 5209–5214.

Schenker, N.M., Buxhoeveden, D.P., Blackmon, W.L., et al., 2008. A comparative quantitative analysis of cytoarchitecture and minicolumnar organization in Broca's area in humans and great apes. Journal of Comparative Neurology 510, 117–128.

Schwarz, F., Springer, S.A., Altheide, T.K., et al., 2015. Human-specific derived alleles of *CD33* and other genes protect against postreproductive cognitive decline. Proceedings of the National Academy of Sciences of the United States of America 113 (1), 74–79.

Semendeferi, K., Damasio, H., Frank, R., Van Hoesen, G.W., 1997. The evolution of the frontal lobes: a volumetric analysis based on three-dimensional reconstructions of magnetic resonance scans of human and ape brains. Journal of Human Evolution 32, 375–388.

Smail, D.L., 2008. On Deep History and the Brain. University of California Press, Berkeley.

Smith, A.R., Carmody, R.N., Dutton, R.J., Wrangham, R.W., 2015. The significance of cooking for early hominin scavenging. Journal of Human Evolution 84, 62–70.

Somel, M., Franz, H., Yan, Z., et al., 2009. Transcriptional neoteny in the human brain. Proceedings of the National Academy of Sciences of the United States of America 106, 5743–5748.

Somel, M., Liu, X., Tang, L., et al., 2011. MicroRNA-driven developmental remodeling in the brain distinguishes humans from other primates. PLoS Biology 9, e1001214.

Stout, D., Chaminade, T., 2007. The evolutionary neuroscience of tool making. Neuropsychologia 45, 1091–1100.

Stout, D., Hecht, E., Khreisheh, N., Bradley, B., Chaminade, T., 2015. Cognitive demands of lower paleolithic toolmaking. PLoS One 10, e0121804.

Sullivan, R.J., Hagen, E.H., 2002. Psychotropic substance-seeking: evolutionary pathology or adaptation. Addiction 97, 389–400.

Tao, N., Wu, S., Kim, J., et al., 2011. Evolutionary glycomics: characterization of milk oligosaccharides in primates. Journal of Proteome Research 10, 1548–1557.

Tennie, C., Call, J., Tomasello, M., 2009. Ratcheting up the ratchet: on the evolution of cumulative culture. Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences 364, 2405–2415.

Tocheri, M.W., Orr, C.M., Jacofsky, M.C., Marzke, M.W., 2008. The evolutionary history of the hominin hand since the last common ancestor of *Pan* and *Homo*. Journal of Anatomy 212, 544–562.

Tomasello, M., Hare, B., Lehmann, H., Call, J., 2007. Reliance on head versus eyes in the gaze following of great apes and human infants: the cooperative eye hypothesis. Journal of Human Evolution 52, 314–320.

Urashima, T., Odaka, G., Asakuma, S., et al., 2009. Chemical characterization of oligosaccharides in chimpanzee, bonobo, gorilla, orangutan, and siamang milk or colostrum. Glycobiology 19, 499–508.

Varki, A., 2010. Colloquium paper: uniquely human evolution of sialic acid genetics and biology. Proceedings of the National Academy of Sciences of the United States of America 107 (Suppl. 2), 8939–8946.

Varki, A., 2013. Thought experiment: dating the origin of us. The Scientist 27, 28–29.

Varki, A., Nelson, D., 2007. Genomic differences between humans and chimpanzees. Annual Review of Anthropology 36, 191–209.

Varki, A., Wills, C., Perlmutter, D., et al., 1998. Great ape phenome project? Science 282, 239–240.

Varki, N., Anderson, D., Herndon, J.G., et al., 2009. Heart disease is common in humans and chimpanzees, but is caused by different pathological processes. Evolutionary Applications 2, 101–112.

Varki, N.M., Strobert, E., Dick, E.J., Benirschke, K., Varki, A., 2011. Biomedical differences between human and nonhuman hominids: potential roles for uniquely human aspects of sialic acid biology. Annual Review of Pathology 6, 365–393.

Varki, N.M., Varki, A., 2015. On the apparent rarity of carcinomas in the "great apes". Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences 34 (22), 2775–2788.

Ventura, M., Catacchio, C.R., Sajjadian, S., Vives, L., Sudmant, P.H., Marques-Bonet, T., Graves, T.A., Wilson, R.K., Eichler, E.E., 2012. The evolution of African great ape subtelomeric heterochromatin and the fusion of human chromosome 2. Genome Research 22, 1036–1049.

Wadley, L., Hodgskiss, T., Grant, M., 2009. From the cover: implications for complex cognition from the hafting of tools with compound adhesives in the Middle Stone Age, South Africa. Proceedings of the National Academy of Sciences of the United States of America 106, 9590–9594.

Walker, A., 2009. The strength of great apes and the speed of humans. Current Anthropology 50, 229–234.

Wiessner, P.W., 2014. Embers of society: firelight talk among the Ju/'hoansi Bushmen. Proceedings of the National Academy of Sciences of the United States of America 111, 14027–14035.

Wobber, V., Herrmann, E., Hare, B., Wrangham, R., Tomasello, M., 2014. Differences in the early cognitive development of children and great apes. Developmental Psychobiology 56, 547–573.

Wrangham, J., Laden, P., Conklin, B., 1999. The raw and the stolen. Cooking and the ecology of human origins. Current Anthropology 40, 567–594.

Chapter 10

Human Intergroup Variation and Disease Genetics

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LIST OF ABBREVIATIONS

AFA African American
AIM Ancestry informative marker
AJ Ashkenazi Jew
CD/CV Common disease/common variant hypothesis
CV Common variant
EURA European American
GWAS Genome Wide Association Study
HLA Human leukocyte antigens
LFV Low frequency variant
MHC Major histocompatibility complex
MRV Multiple rare variant hypothesis
OOA Out-of-Africa
RV Rare variant
SCZ Schizophrenia
SRA Self-reported ancestry
VBD Vector-borne diseases
WES Whole exome sequencing
WGS Whole genome sequencing

INTRODUCTION

In the last 30 years, human genetic variation at the individual and population levels has received considerable research attention. The need to shed light on human evolution is of course a goal in itself. However, the findings of applied research constitute a major targeted pay-off of this exploration. It appears that most of, if not all, human diseases result from both the environment in the broad sense and the genetic background of individuals and populations, as indeed it would be the case for any phenotype. Exploring human genetic variability in depth therefore appears to be a major hope for finding radical cures for disease and drug resistance, leading us toward the ultimate end target of personalized medicine (Lee and Mudaliar, 2009).

The present chapter does not claim to be a comprehensive review of the topic, but instead aims to describe the most recent advances and the main currents in this field. With the impressive technological advances made in recent years, exploring the genetic background of pathological traits is progressing very rapidly, so that data from a few years ago may be outdated. Moreover, this chapter will focus on disease gene diversity at the population rather than the individual level. Indeed, (1) group comparisons are highly relevant where preventive medicine, which focuses on populations more than on individuals, is concerned. Consequently, the recommendations made by Lee et al. (2008) for "maintaining focus on the individual rather than the group" are adapted for individual medicine but not for preventive medicine, which should look for group characteristics, and as we will see in this chapter, (2) the most remarkable feature of the genetic background of pathological traits is that they are unevenly distributed throughout the world. This is not unexpected, since different populations have undergone radically dissimilar selective pressures in diversified environments since the out-of-Africa (OOA) migrations.

BRIEF REVIEW OF POPULATION STRUCTURE AND RECENT EVOLUTION IN HUMANS

An evolutionary view of medicine requires insight into human genetic and genomic variability, not only at the individual level, but also at the population scale. Different human groups after the major OOA migrations have

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00010-7

undergone radically different selective pressures in highly diversified environments (in terms of climate, food sources, and pathogen burden). It can therefore be expected that, together with a common background, pathological profiles of human populations will exhibit group differences.

Human population structure and recent evolution have been developed at length in Chapter 6. Only a brief review will be provided here.

Since pioneering studies of the late 1970s (Nei, 1978), high-resolution genetic markers have been massively used for the study of human populations. Today, studies using several 100,000 single-nucleotide polymorphisms (SNPs) are not exceptional (Li et al., 2008; López Herráez et al., 2009). Convergent results have been gathered through these studies. They can be summarized as follows:

1. When common (frequency $\geq$5%) markers that do not undergo natural selection ("neutral") are considered, most (from 85% to 95% depending on the marker) human genetic variability is found within continental groups (eg, within Sub-Saharan Africa) rather than between them (eg, Africa vs. Europe).
2. The use of randomly selected markers makes it possible to uncover major continental groups (in general, Africa, Europe, Asia, Oceania, and the Americas), which confirms early studies that investigated low-resolution markers (Nei, 1978). The groups revealed by genetic labeling are not strictly separated and show some overlapping.
3. When a large number of high-resolution power markers are used, ancestry and degree of admixture of individuals can be reliably inferred, in particular using ancestry informative markers (AIMs).
4. Modern markers reveal a high stratification (Russian doll pattern; Tibayrenc and Ayala, 2013) within major continental groups. These major groups are far from being uniform and show many subgroups and/or clinal patterns related to geographical distance, geographical obstacles, and cultural (linguistic) barriers.
5. Low-frequency genetic variants (LFVs) (frequency ranging from 0.5% to 5%) and even more, rare variants (RVs) (frequency lower than 0.5%) are far more numerous than common variants (CVs). LFVs and RVs are recent, geographically localized, and are assumed to play a major role in phenotypic and disease variability.
6. Copy number variation (CNV), gene regulation, epigenetics, and epistasis also have a major role in phenotypes and disease, more than coding variation (which commands protein synthesis).
7. Lastly, evidence for abundant, geographically localized, recent adaptation is growing: it seems that natural selection has not stopped with the advent of modern humans 40,000−50,000 years ago, as was classically believed, but rather has strongly acted on human populations until recently, and probably still does.

This brief summary gives us the picture necessary to consider disease burden in humans at the population level. One could adopt the approach of directly looking for the genes suspected of being responsible for disorders. It is instead recommended to first establish a general picture of the population structure of the human groups under survey, and then to see where the disease genes map onto this general framework. A clear view on the relationships between disease genetic background and the overall evolution of the species under study can be thus obtained (phylogenetic character mapping, PCM; Avise, 2004).

LOOKING FOR DISEASE GENES: CANDIDATE GENES, GWAS, WGS; CD/CV, RV

The search for disease genes makes use of different strategies according to the kind of disease involved. The easiest case is that of Mendelian diseases, where only one gene, inherited according to Mendelian laws, is the culprit. The search is easier when the penetrance of the gene is strong. A typical case of Mendelian disease is sickle cell anemia (see "Transmissible Diseases" in this chapter). Unfortunately, Mendelian diseases are the exception rather than the rule. Most diseases (complex diseases) are commanded by many genes, the penetrance of each being low (see the infinitesimal model, Fisher, 1918), and are influenced by both genetics and the environment. It seems that LFVs and RVs (see earlier and Chapter 6), as well as CNV, gene regulation, epigenetics, and epistasis, play a major role in complex diseases. All this makes elucidating the genetic command of complex diseases a tough job. It will be more or less arduous depending on the transmission model of the disease. The common disease/common variant (CD/CV) hypothesis postulates that the genetic factors involved are evenly distributed among populations and are CVs (frequency $\geq$5%). The multiple rare variant (MRV) hypothesis, on the other hand, considers that most complex diseases are caused by RVs or LFVs (Keita et al., 2004). As we will see, many if not most diseases have uneven geographical distributions and are caused by RVs or LFVs. This strongly influences the methods used to look for the genetic background of diseases.

In the candidate gene approach, the working hypothesis is that a given gene or a given set of genes is responsible for a given disease. For example, a given gene or set of genes is suspected because it is associated with biological processes that frequently play a role in the disease under study.

With transmissible diseases, this is the case for the genes that are involved in immunological defense, in particular the genes that belong to the major histocompatibility complex (MHC), which are referred to as human leukocyte antigens (HLA) in the human species. These families of genes are therefore frequently analyzed when the putative genetic background of a given infectious process is explored. Another case is when a homologous gene plays an important role in infectious processes in animal models. However, this last deduction may well be wrong. Indeed, comparable gene sequences may encode totally different functions in different animal species (Blackwell, 1996): "Evolution is constantly re-using old genes for new purposes" (Birky, 2009).

In the "linkage approach," a specific segment of the genome is identified through whole genome mapping (Genome-Wide Association Study, GWAS), with a broad set of microsatellite markers or, increasingly today, SNPs, and association analyses based on twin sib pair, family, or pedigree studies. The null hypothesis is a total lack of linkage disequilibrium between the explored trait (disease) and the DNA segment. If, on the contrary, linkage disequilibrium is strong, this suggests that the region identified by the microsatellite or SNP mapping contains genes that are involved in the pathology under survey.

Lastly, the search for disease genes is increasingly based on high-throughput whole-genome sequencing (WGS). When the MRV hypothesis is verified, both the candidate gene approach and the GWAS often miss the target.

Let us now consider how diseases and their genes are distributed among populations throughout the world.

MENDELIAN DISEASES AROUND THE WORLD

Most Mendelian disorders have a recessive mode of transmission (only homozygous subjects suffer from the disease). If the deleterious allele is dominant (both homozygous and heterozygous subjects are ill), it would be rapidly eliminated.

According to Jorde and Wooding (2004), Mendelian (single-gene) diseases are the ones that show the clearest distinctions among geographical populations, although population differences are seen for common diseases as well. Gonzaga-Jauregui et al. (2012) stated that whole-exome sequencing (WES) was able to detect genes involved in Mendelian diseases. However, WES ignores 98% of the genome, and this neglected part is probably highly relevant for disease studies. Using WES, Fu et al. (2013) found that Europeans had an excess of deleterious alleles linked to Mendelian diseases compared to African Americans (AFAs). SNPs linked to Mendelian disorders tended to be RVs (Fu et al., 2013), which suggests that they are geographically restricted, and of recent origin (The 1000 Genomes Project Consortium, 2012). Some examples of Mendelian diseases with uneven distribution among geographical populations are presented below.

- Phenylketonuria is a classic case of a Mendelian disorder. Only one mutation in the phenylalanine hydroxylase (*PAH*) gene has dramatic consequences on ill children, who suffer from mental retardation. However, an appropriate phenylalanine-free diet is enough to counter the negative effects of the disease. This shows that even a typical Mendelian disorder can be profoundly modulated by environmental parameters. The distribution of the disease is not balanced among populations of different ancestries. In a UK survey, birth prevalence per 10,000 live births was estimated to be 1.14 (0.96−1.33) among Europeans, 0.11 (0.02−0.37) among Africans, and 0.29 (0.10−0.63) among Asians (Hardelid et al., 2008).
- Cystic fibrosis and hemochromatosis are other Mendelian disorders whose geographic distribution is quite uneven. Cystic fibrosis is the result of a mutation in both copies of the *CFTR* gene, the cystic fibrosis transmembrane conductance regulator protein. This leads to a hypersecretion of thick mucus in the lungs, multiple lung infections, and respiratory insufficiency. Hereditary hemochromatosis results from excess iron absorption from the food. Iron is stocked in the pancreas, heart, and liver, and these organs may become damaged. Most cases are caused by a mutation in the High Iron Fe (*HFE*) gene. Both cystic fibrosis and hemochromatosis are much more frequent in Europe than in other parts of the world (González Burchard et al., 2003; Jorde and Wooding, 2004; Mersha and Abebe, 2015; Mountain and Risch, 2004; Risch et al., 2002; Spielman et al., 2007). It does not mean that this disease does not exist outside Europe. Cystic fibrosis could be linked to a phenomenon of balanced selection (that is to say, the homozygotes are ill, while the heterozygotes are advantageous). As a matter of fact, it has been hypothesized that heterozygous individuals could be protected from cholera to some extent (Jordan, 2008, Chapter 4).
- Factor V Leiden thrombophilia, which provokes a blood clotting disorder, is the result of a single mutation of the Factor V (*F5*) gene. Contrary to many Mendelian disorders, it is a dominant trait. However, its penetrance is incomplete. This mutation has a frequency of 5% in people of European ancestry and is virtually absent in other populations (Jordan, 2008, Chapter 11).
- Jewish communities, especially Ashkenazi Jews (AJs), suffer from a heavy burden of Mendelian diseases. Several of them are linked to sphingolipid storage

disorders: Tay-Sachs, Gaucher, Niemann-Pick, mucolipidosis type IV (Cochran et al., 2006). Cystic fibrosis, which is present at much higher rates in people of European ancestry than in Africans and Asians (see earlier in this section) is particularly frequent in AJs (Guha et al., 2012). So is Usher syndrome, a rare genetic disorder that leads to visual impairment and hearing loss (Guha et al., 2012). These high rates of Mendelian disorders in AJs are classically assumed to result from a founder effect (present AJ communities were founded by a limited number of individuals) and endogamy. For many centuries, Jews have usually married Jews both for religious reasons and because of discrimination against them. An innovative hypothesis has been proposed by Cochran et al. (2006). A high rate of Mendelian disorders linked to the sphingolipid storage pathway could be the result of a balanced selection process. The advantage for heterozygous subjects would be a high IQ. Indeed, the average IQ in AJs is 115, while it is 100 in other people of European ancestry. In Europe, for historical reasons, AJs specialized in jobs related to money trade, requiring high intellectual ability. This, together with endogamy and reproductive success (at that time, richer people had more children) may have established the conditions for fast selective pressure. Cochran and Harpending (2009, Chapter 7) noted that in Israel, the percentage of Gaucher disease patients having top jobs was 11 times higher than in the general population. Whatever explanation holds true for Mendelian disorders in their community, three important features should be underlined about AJs and disease:

- AJs constitute a relevant target population for the GWAS, since they are genetically rather homogeneous, with little stratification (Guha et al., 2012), both in Israel and the United States.
- The AJ community has been pioneering in personalized medicine, with extensive screening for Mendelian disorders and early breast cancer surgery (Ostrer and Skorecki, 2013).
- The illustrative case of AJs shows that in disease surveys, major continental groups may often be too broad proxies. Subgroup-specific features should be looked for within major continental groups in many cases, due to the Russian doll structure of human populations (see "Brief Review on Population Structure and Recent Evolution in Humans") and the fact that natural selection can specifically act at fine geographic and population scales. The relevance of considering stratification within major geographical groups for both evolution and disease studies was underlined by Barbujani and Colonna (2010), Chapman and Hill (2012), and Rosenberg et al. (2005).

Mendelian disorders linked to transmissible diseases (eg, sickle cell anemia) will be treated separately (see "Transmissible Diseases").

GEOGRAPHICAL DISTRIBUTION OF COMPLEX DISEASES

Complex diseases are also called common diseases, because they are much more numerous than Mendelian disorders. Exploring these diseases is a challenge for two reasons: (1) many different genes, each having a weak impact, may be involved in their etiology and (2) environmental causes play a major role in many, if not most, complex disorders. Although modern genomics is more efficient for exploring Mendelian traits (Cavalli Sforza, 2007), it has contributed to significant progress in elucidating the genetic background of complex diseases. Without modern genomic tools, it would have been extremely difficult to separate environmental from genetic causes.

Complex diseases, such as hypertension, diabetes, and obesity, differ in frequency across ethnic groups (Tishkoff and Kidd, 2004). According to Tennessen et al. (2012), RVs and LFVs could explain most of the heritability of common diseases and CVs would account for only a modest proportion of the heritability of most traits. Spielman et al. (2007) have proposed that differences in gene expression in different ethnic groups could account for prevalence differences of complex diseases (diabetes, high blood pressure) in these populations.

We will consider below cardiovascular diseases, diabetes, psychological disorders and mental illness, respiratory diseases, and cancer. Autoimmune disorders will be treated with transmissible diseases.

Cardiovascular Diseases

In cardiovascular diseases distinguishing between environmental and genetic factors is a challenge. Indeed, it is well known that lifestyle (smoking, diet, exercise, weight) plays a major role in these disorders. However, it is indisputable that the genetic background has a strong impact as well, and that this impact strikes different ancestry groups unevenly.

High blood pressure is more frequent in AFAs than in European Americans (EURAs); consequently, patient ancestry should be taken into account in cardiovascular disease management (Betancourt and López, 1993; Sarich and Miele, 2004, Chapter 7). According to Tate and Goldstein (2004), AFAs have twice as many heart attacks as EURAs. Helgadottir et al. (2006) found that the *HapK* haplotype of the Leukotriene A4 hydrolase (*LTA4H*) gene increased the risk of myocardial infarction three times more in AFAs than in EURAs. The presence of this variant

in AFAs is due to European admixture, since it is very rare in Africa.

Within the African Genome Variation Project, Gurdasani et al. (2015) showed high frequency differences between Europeans and Africans for loci under selection related to hypertension susceptibility. These genes could be related to the high burden of hypertension and differences in salt sensitivity observed in Sub-Saharan Africa (Gurdasani et al., 2015). This would confirm the hypothesis proposed by Laland et al. (2010) that populations after the OOA migrations underwent different selective pressures for salt sensitivity related to adaptation to different climates. According to Miller (1994), the high rate of hypertension in AFAs could be attributable to a selective advantage that the genes responsible for it confer in malaria-endemic areas. One of the origins of the higher burden of hypertension in AFAs is kidney disease. A polymorphism at the Apolipoprotein L1 (*APOL1*) gene could be responsible for this higher frequency of kidney diseases and would be a case of balanced selection. It may be involved in resistance to human African trypanosomiasis, also known as sleeping sickness (Karlsson et al., 2014; Lachance and Tishkoff, 2013; Lander, 2011).

Ayub et al. (2013) surveyed signals of positive selection on the target genes of the transcription factor FOXP2. They found that overall there was evidence for strong selection for these target genes in their European sample but not in the African and Asian samples. Intriguingly, among the target genes identified as significant outliers in the European sample, there were 13 genes associated with cardiac arteriopathy (Ayub et al., 2013).

Diabetes and the Thrifty Hypothesis

Type 2 diabetes (noninsulin-dependent diabetes mellitus, or NIDDM) is a polygenic disease strongly influenced by environmental parameters (diet, weight, lifestyle). Its heritability is only 35% (Hyman, 2014). It is quite different from type 1 diabetes, which strikes infants, is an autoimmune disease in 90% of cases, and will therefore be discussed with other autoimmune disorders. The thrifty hypothesis (Neel, 1962) proposes that the genotype of modern populations is not adequately adapted to present diet conditions, which leads to the diseases of modernity, with type 2 diabetes a leading example. The episodic starving undergone by ancestral hunter-gatherer populations is hypothesized to have led to a strong selection for lipid storage, which is a disaster in this McDonald's world. The thrifty hypothesis has been invoked to explain high rates of type 2 diabetes in Polynesians, whose ancestors are thought to have undergone starvation during their long-term ocean voyages (Laland et al., 2010). Cochran and Harpending (2009, Chapter 3) challenged the thrifty hypothesis. They observed that starving was certainly more frequent in early agricultural societies than in hunter-gatherer groups. The last hunter-gatherers in existence today do not suffer from starving. According to these authors, the rate of type 2 diabetes is 2.5 times higher in Navajo Native Americans and four times higher in Australian natives than in Europeans. This is assumed to be caused by these populations adapting too late to the diet of agricultural societies, which is richer in carbohydrates than the food of the hunter-gatherers.

Fraser (2013) found that the frequency of type 2 diabetes risk alleles was negatively correlated with the distance to the equator, which suggests that alleles that are advantageous in cold climates confer protection to type 2 diabetes alleles and does not argue in favor of the thrifty hypothesis. Whatever the historical reasons, type 2 diabetes and its genetic risk background are quite unevenly distributed among geographical populations.

Corona et al. (2013) calculated the genetic risk of 102 diseases in 1043 individuals in 51 populations. They found that the genetic risk for type 2 diabetes was the highest in African populations, followed by the populations of Europe, the Middle East, and Asia. According to González Burchard et al. (2003), the rate of complications from type 2 diabetes is ancestry-dependent in members of the same health organization, in spite of homogeneous services and after adjustment for levels of education and income, health behavior, and clinical characteristics. The same authors reported that in Pima Native Americans, the degree of European admixture as estimated by self-reported ancestry (SRA) was strongly correlated with protection from type 2 diabetes. Heyn et al. (2013) found that DNA methylation (a process of gene regulation) could influence the difference of susceptibility to type 2 diabetes in human populations. Differential methylation was observed in genes [*HLA-B/C*, Protein Kinase C, Zeta (*PRKCZ*)] related to the different penetrance of type 2 diabetes in distinct human groups. Pickrell et al. (2009) found that the frequencies of the genomic regions associated with type 2 diabetes risk were clearly differentiated in different geographical populations. The level of statistical significance for these differences was $p = 0.006$ for Europe versus Africa, and $p = 0.02$ for East Asia versus Africa.

Psychological Disorders and Mental Illness

This section concerns only those mental traits that are generally considered as pathological. Stories on brain genes, cognition, and behavioral differences are presented in Chapter 6. The border between "normal" and "pathological" is sometimes blurred where brain functioning is concerned, as has been masterfully explained by Frances (2013). The thresholds for defining psychiatric illness, as established by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), are arbitrary (Hyman, 2014).

This is the case for many, if not all, thresholds used in medicine, such as threshold levels on hypertension. However, hypertension is a much simpler parameter than schizophrenia (SCZ) or autism spectrum disorder (ASD), and its epidemiological risks have been thoroughly studied.

The heritability of major psychological disorders is far from being negligible: it is 35% for depression and up to 65−80% for SCZ (Hyman, 2014). Looking for risk variants is challenging, due to the unclear definition of many syndromes. However, it gives the hope of finding new drugs (Hyman, 2014). Associations between genetic variants and increased risk for SCZ, ASD, major depression, and bipolar disorder (BPD) have been fully confirmed. In most cases, the loci identified by the GWAS involve regulatory regions rather than specific genes (Geschwind and Flint, 2015). It is probable that many risk variants are shared among several mental disorders, as is the case between autoimmune and inflammatory diseases (Hyman, 2014). In fact, inflammatory and immunity genes are associated with psychiatric diseases, including SCZ and ASD (Karlsson et al., 2014). Genetic findings blur the boundaries between psychiatric diseases, as well as the limits between normal and pathological. It seems that the increased polygenic risk for BPD and SCZ favors creativity. In patients' families, there are individuals who are not ill and exhibit intermediary phenotypes or "endophenotypes" (Geschwind and Flint, 2015). Identifying the precise genetic background of mental illnesses could lead to a nosological redefinition of these diseases, from symptomatological to causal (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Geschwind and Flint, 2015).

This chapter focuses on differences among geographical populations. Unfortunately, fishing for population-specific psychological disorder variation may provide a meager catch: "The vast preponderance of psychiatric genetic data comes from Europeans, having relied on Scandinavian population registries, and European national health systems" (Steven Hyman, personal communication). Empirical evidence for differences in mental illness prevalence among groups of different ancestries is available (Harris et al., 2005; Williams et al., 2007). Differences in mental illness prevalence among ancestral groups is confirmed by the data from the US Centers for Disease Control (CDC; see http://www.cdc.gov/mentalhealth/basics/burden.htm). However, these rough data are not evidence for genetic causes of these prevalence differences, since obvious environmental parameters (sociological, economic, familial) certainly play a major role in mental illness etiology. In the two following cases, genetic data are available.

The genetic background of SCZ appears to be complex. Rare deletions (Lander, 2011), CVs (Lander, 2011; Zietsch et al., 2015), and microdeletions at specific loci in the *22q11.2*, *1q21.1*, and *15q13.3* chromosomes (Belizário, 2013) have been incriminated, as well as rare CNVs (Gonzaga-Jauregui et al., 2012). No common CNVs are known to be associated with SCZ (Zietsch et al., 2015). The Dystrobrevin Binding Protein 1 (*DTNBP1*) gene on the sixth chromosome has been demonstrated to have an impact on SCZ risk and may also influence general cognitive ability (Burdick et al., 2006). Regulatory phenomena are also involved in the etiology of SCZ (Geschwind and Flint, 2015). Lastly, inflammatory and immunity genes are associated with SCZ (Karlsson et al., 2014). When differences among populations are involved, the broad GWAS based on CV tagging suggests that many SCZ risk alleles are shared across ethnic groups and predate African-European divergence (de Candia et al., 2013). However, this study deals with CVs only and does not consider the possible role played by RVs, which tend to be geographically restricted. Common variation is considered to account for more than 33% of SCZ heritability (Lander, 2011).

Alzheimer's disease is known to show uneven frequencies among populations of different ancestries (Armengol et al., 2009; Farrer et al., 1997). The Apolipoprotein E (*APOE*) gene and its ε variants play a major role in the etiology of the disease. The *APOEε4* variant is recorded in all geographical populations, although with different frequencies: Japanese 9%, Europeans 14%, and AFAs 19% (González Burchard et al., 2003). Homozygosity of the *ε4* allele increases the risk of Alzheimer's disease by a factor of 33 in Japanese individuals, 15 in Europeans, and 6 in AFAs. For heterozygous subjects, the figures are 5.6, 3.0, and 1.1, respectively (González Burchard et al., 2003). Rare and common CNVs are also incriminated in Alzheimer's etiology (Armengol et al., 2009; Gonzaga-Jauregui et al., 2012). If rare CNVs play a role in Alzheimer's disease, this should increase a differential geographic distribution of the disease, since RVs tend to be population-specific.

Respiratory Diseases: Asthma

Burchard et al. (2015) noted that studies including well-analyzed minorities were dramatically underrepresented in grants dealing with respiratory diseases supported by the National Institutes of Health (NIH), while genetic and environmental risk factors varied dramatically across racial and ethnic groups. These authors warned that this lack of knowledge ultimately had considerable financial costs. As proposed by Bustamante et al. (2011), evaluating the degree of admixture is crucial for proper medical care. In respiratory diseases, physicians compare measurements of lung function (using a spirometer) to a reference standard for healthy people of the same gender and the same

ancestry. The diagnosis is better when the actual genetic ancestry is known. This means that the limits of normal respiratory capacity are not the same among groups of different ancestries, a crucial fact for respiratory disease care. Pulmonary function tests (PFTs) are important parameters for asthma care. In Mexican Americans, European ancestry is associated with more severe asthma, as measured by PFTs (Mersha and Abebe, 2015). According to Moreno-Estrada et al. (2014), depending on one's ancestry background, the same value of forced expiratory volume per second (a classical measure of lung function) could be considered as either normal or indicative of pulmonary disease. These authors found a significant association between lung function and degree of admixture in Mexican populations. It has been proposed that populations of tropical ancestry introduced into temperate regions had a higher risk of developing asthma, as is the case for AFAs and Asians living in the United Kingdom (Vasseur and Quintana-Murci, 2013). Ancestry may have a higher impact than environment on differences in the prevalence of asthma (Vasseur and Quintana-Murci, 2013).

Cancer

Group Differences in Various Forms of Cancer

According to the US CDC, the rate of cancer varies widely among ancestral groups in the United States (http://www.cdc.gov/cancer/dcpc/data/ethnic.htm). The impact of ancestry has been confirmed for the prevalence of the following forms of cancer: breast (Need et al., 2009; Ostrer and Skorecki, 2013; Vasseur and Quintana-Murci, 2013), prostate (Keita et al., 2004), bladder, pancreas (Corona et al., 2013), and skin (melanoma) (Harris, 2015; Shendure and Akey, 2015). AFA males have a 60% greater risk of developing prostate cancer, twice the risk of developing its aggressive form and twice the mortality relative to EURAs. However, geographical, environmental, and genetic parameters should be separated out in this rough statistical data (Keita et al., 2004). According to Corona et al. (2013), the risk of pancreatic cancer diminished as humans migrated toward Asia. This genetic risk is highly variable among geographical populations worldwide, as is the genetic risk for bladder cancer (Corona et al., 2013).

Leukemia

Ancestry matters in the cure of infant lymphoblastic leukemia. Children with more than 10% Native American ancestry need an additional round of chemotherapy for the treatment to be successful (Bustamante et al., 2011; Mersha and Abebe, 2015).

Melanoma

According to Harris (2015), the somatic mutation 5′-TCC-3′ → 5′-TTC-3′ is a specific signature for melanoma, which is the most malignant form of cancer. Melanoma is associated with ultraviolet (UV) radiation exposure, but also with ancestry. The annual age-adjusted incidence of melanoma cases per 100,000 people is 0.8−0.9 for Asians, 0.7−1.0 for AFAs, and 11.3−17.2 for EURAs. Melanoma incidence in Hispanics is strongly correlated with European admixture. The transition TCC → T has been found in the five European subpopulations of the 1000 genome project: Italians (TSI), Spanish (IBS), Utah residents of European descent (CEU), British (GBR), and Finnish (FIN). Its increasing frequency in Europeans is assumed to have occurred in the last 40,000 to 80,000 years, after Europeans started diverging from Asians (Harris, 2015).

Breast Cancer

Migrant studies are informative to distinguish between environmental and genetic parameters in disease etiology. The incidence of breast cancer is lower in Asian than in European women. In Asian-American women, this difference disappears, which indicates a strong environmental component (Risch et al., 2002). However, susceptibility breast cancer genes (*BRCA1* and *BRCA2*) have been clearly evidenced in hereditary forms of breast cancer and explain the high incidence of this disease in AJs (Need et al., 2009; Ostrer and Skorecki, 2013). The Glucuronosyltransferase 2 Family, Polypeptide B4 (*UGT2B4*) gene has been strongly associated with increased risk of breast cancer in Nigerians and to a lesser extent in AFAs (Vasseur and Quintana-Murci, 2013).

From the above discussions, it is quite clear that genetic ancestry is a parameter to be taken into account in disease etiology, not only in Mendelian disorders, but also in complex, common diseases. It can therefore only be claimed tentatively that life conditions are responsible for most of the differences observed in disease incidence between different communities in the United States (Jordan, 2008, Chapter 11). Culture, education, environment, lifestyle, economic conditions, and access to health care should undoubtedly be carefully taken into account in this matter. All physicians are aware of this. However, attributing only a minor role to genes could be misleading. The progress of genomics will make it possible to clarify this question, to directly evidence the genetic backgrounds that can be incriminated in disease disparities among populations of different ancestries, and at the same time to show what stems mainly from environmental parameters. As we have seen, admixed populations are an informative tool for deciphering the genetic background of disease

causes. Lastly, with their very specific disease burden, the case of AJs illustrates that major geographical groups could be excessively broad proxies in many cases for considering the genetic basis of diseases. The relevance of studying such ancestry subgroups and admixed populations as well will again be underlined in the case of transmissible diseases.

TRANSMISSIBLE DISEASES, STILL THE MAIN FACTOR OF NATURAL SELECTION IN HUMANS

In this section we will consider: (1) human genetic susceptibility to infectious diseases, a coevolution phenomenon between the host, the pathogen, and the vector in vector-borne diseases (VBDs); (2) autoimmune and inflammatory diseases, which seem to be linked to pathogen selective pressure (the hygiene hypothesis).

Transmissible diseases can be caused by: (1) viruses (eg, AIDS, yellow fever); (2) bacteria (eg, tuberculosis, typhoid fever); (3) parasitic protozoa (eg, malaria, sleeping sickness); (4) yeasts and fungi (eg, cryptococcosis, candidosis); and (5) parasitic helminths (eg, river blindness, taeniasis).

Coevolution Between Humans and Pathogens: A Red Queen Story

Selective Pressure and Agriculture

Haldane (1949) proposed that transmissible diseases have been the strongest selective pressure on humankind in the last 5000 years. This selective pressure is assumed to have played an important role mainly in malaria in Africa and tuberculosis in Europe (Miller, 1994). Historical epidemics such as the black plague, or more recently the Spanish flu, which killed tens of millions of people, had considerable demographic consequences. However, it is probable that endemic diseases such as malaria and tuberculosis, which act continuously over thousands of years, and massively strike young subjects, have a stronger selective effect. In fact, it is probable that the selective impact of transmissible diseases is much older than 5000 years and acted throughout the evolutionary process of the human species. However, epidemics spread more easily in human populations grouped in large communities than in the scattered, small pre-Neolithic hunter-gatherer populations. Cochran and Harpending (2009, Chapter 4) hypothesized that the advent of agriculture, accompanied by domestication of animals (acting as disease reservoirs) and the increase in trade and travel boosted the selective pressure of infectious diseases on humans.

Human Leukocyte Antigen Features

Strong evidence of the impact of transmissible diseases on human evolution is the particular genetic pattern of the HLA system. Some HLA human alleles have a very ancient coalescence time, prior to the evolutionary split among Old World monkeys, and are genetically closer to some *Macacus* alleles than to other human HLA alleles. Ayala and Escalante (1996) hypothesized that this was due to balanced selection by pathogens, mainly malaria. Since malaria exerted its strongest selective pressure in Africa, people of African and European descent have very different HLA polymorphisms. Before the advent of sequence characterization, HLA typing in AFAs lacked precision, which was the cause of a higher rate of organ transplant rejections in this group. According to Fu and Akey (2013) and Racimo et al. (2015), archaic adaptive introgression (AAI) (capture by modern humans of some genomic parts from Neandertals and Denisovans through limited admixture) played a major role in shaping the HLA polymorphism of non-African populations.

Coevolution and the Red Queen Hypothesis

Since the advent of mankind, our species has undergone a constant race with pathogens, according to the "red queen hypothesis" (Van Valen, 1973): "Those who do not move on, move back." The host had to constantly adapt to its pathogens, and the pathogens had to succeed in being transmitted. The pathogen panoply of a given host (here, humans) can be considered to be a characteristic, a phenotype of the host, and vice-versa (Tibayrenc, 1998). A third partner, the vector, enters the dance in the case of VBDs such as malaria and yellow fever. All this is a complex phenomenon of coevolution. Many parts of our genome have been shaped by this race and continue to be so influenced. Infectious diseases still impose their tax on humankind. Every year, they cause the death of millions of babies and infants, mainly in tropical areas and low-income countries. It is logical to infer that survivors are better armed genetically to face the pathogen challenge.

Geographical Differences

It is also logical to assume that populations living in different geographical areas, hosting different pathogen and vector species, had to adapt accordingly (Tibayrenc, 2004, 2007a,b). In Medieval times, malaria raged as far north as Flanders, and it continues to be transmitted in Corsica. However, this is the mild malaria caused by the parasite *Plasmodium vivax*. Europe never had to confront the threat of the serial killer *Plasmodium falciparum*. It is obvious that all transmissible diseases exhibit a strongly differential geographical distribution (Gentillini et al., 2012). So the

selective pressure of pathogens on humans has been quite uneven. Prugnolle et al. (2005) proposed that HLA polymorphism paralleled pathogen diversity in different countries. In the same population, there can be considerable individual differences in genetic susceptibility to infectious diseases (Abel and Dessein, 1997), as in all diseases. However, especially in the case of transmissible diseases, group differences, which are the main theme of this chapter, deserve to be explored in depth.

Infectious Diseases and History

Cochran and Harpending (2009, Chapter 6) proposed that this uneven distribution of disease resistance genes in human populations had a strong impact on historical events. The Spanish conquistadores had to fight against well-trained Native American armies, the Incas and the Aztecs, who were infinitely more numerous. Of course the Spaniards had (primitive) firearms. However, they brought in their luggage a better weapon, namely European infectious diseases, to which Native Americans were immunologically naïve. Bacteria more than muskets and blunderbusses committed a Native American genocide that may have considerably facilitated the Spanish *conquista.* Later, European colonization in Africa may have been slowed down by tropical diseases the Europeans were not adapted to.

Before this, Arab penetration into Africa may have been stopped by sleeping sickness. It is notable that the limits of Islam in Africa are more or less those of the area of distribution of this disease's vector, the tsetse fly (*Glossina* spp.).

Let us now have a closer look at how much genetic susceptibility to different transmissible diseases varies around the world.

Different Populations, Different Diseases, Different Genes

Malaria

Malaria is our number one assassin. It is caused by four different species of blood parasites, *Plasmodium falciparum* (the most harmful form of the disease), *P. vivax*, *P. malariae*, and *P. ovale*. Malaria is a strict VBD. Its vectors are anopheline mosquitoes. The bulk of transmission occurs between the tropics or at least in warm countries, Africa being the main victim. This can be seen in human genes. Threatened populations have developed a genetic arsenal for resisting malaria. According to Cochan and Harpending (2009, Chapter 5), Phoenician and Roman colonization around the Mediterranean may have contributed to disseminating the pathogen. According to Tishkoff (2015), human populations exhibit geographically localized adaptive traits of malaria resistance. The most classic case is sickle cell anemia, which is a paradigmatic example of balanced selection. Homozygous individuals suffer from a very severe form of the anemia, while heterozygous individuals, who are much more numerous, have no anemia and are protected from malaria (Allison, 1956). It is remarkable that the genetic trait persisted in AFAs, who have not faced *falciparum* malaria for centuries. Melanesian ovalocytosis (Tanner et al., 1991) is another disease in which heterozygous individuals are protected from malaria. Malaria's area of distribution parallels that of not only sickle cell anemia and ovalocytosis, but also α-thalassemia and glucose 6-phosphate dehydrogenase deficiency, which are also involved in the defense against this disease (Karlsson et al., 2014). Less classic genetic mechanisms involved in malaria resistance have been uncovered. The Duffy antigen receptor for chemokines (*DARC*) gene, which codes for the Duffy blood group antigen O allele, is associated with resistance to malaria in Africans. Its rs2814778 variant seems to have undergone recent positive selection (Colonna et al., 2014). Many deletions (including in genes such as globins and Solute Carrier Family 4 (Anion Exchanger), Member 1 (*SCL4A1*)) are found only in regions where malaria is endemic because they confer resistance to malaria (Conrad and Hurles, 2007). Daub et al. (2013) looked for selection, not at the level of independent genes, but instead at the level of pathway gene sets. Their approach was based on population differentiation (*F*st; see Chapter 6) computed for many populations worldwide. They found indications of polygenic positive selection (and hence, strong geographical differentiation, as revealed by *F*st analysis) for malaria pathway genes, some of which were already known. New loci under positive selection linked to malaria resistance were identified by Gurdasani et al. (2015). Malaria shows an interesting case of specific genetic resistance of a particular human subgroup. The Fulani, who are West African pastoralists, resist the disease much better than other African groups (Mossi) with whom they live in sympatry (Modiano et al., 1999). As already noted in the case of AJs, this shows that disease studies should look for stratification and subgroups within the major human continental groups.

AIDS

The disease is caused by HIV-1 and -2 (human immunodeficiency virus). It shows a counterintuitive case of genetic resistance, since Africans appear to be more vulnerable to AIDS than Europeans. The hypothesis to explain this feature is based on allelic frequency differences for a deletion in the *CCR-5* chemokine receptor gene. This deletion (CCR5Δ32) is much more frequent in Europeans

than in Africans (Dean et al., 1996). Individuals who are heterozygous for CCR5Δ32 have a slower disease progression. Moreover, individuals homozygous for CCR5Δ32 (about 1% of Europeans) are highly resistant to acquiring HIV-1 infection, even after multiple exposures (Chapman and Hill, 2012). At the genomic level, extreme population differentiation was noted for the CNV of the Chemokine (C−C motif) ligand 3-like 1 *CCL3L1* polymorphism, which also influences human susceptibility to HIV infection (Conrad and Hurles, 2007; Gonzalez et al., 2005). Rare CNVs (hence bound to be geographically restricted) also seem to be involved in HIV susceptibility (Gonzaga-Jauregui et al., 2012). Heyn et al. (2013) compared the methylation profiles (involved in gene regulation) of the β-lymphocytes of 96 AFAs, 96 EURAs, and 96 Han Chinese. They found population-specific methylation profiles for genes associated with different disease penetrance levels, including AIDS. Grossman et al. (2013) identified various polymorphisms having undergone recent evolution (and therefore likely to be geographically restricted), associated with susceptibility to infectious diseases. Among them were two genes related to HIV infection, namely tyrosyl protein sulfotransferase 1 (*TPST1*) and C-X-C chemokine receptor type 4 (*CXCR4*). Much remains to be learned in the genetics of HIV susceptibility. Taken together, HLA class I loci and the CCR5 polymorphism account for 23% of the observed variability of HIV control only (Chapman and Hill, 2012).

Human African Trypanosomiasis

Human African trypanosomiasis (HAT; formerly sleeping sickness) is one of the most devastating transmissible diseases of Sub-Saharan Africa. It is caused by the parasitic protozoan *Trypanosoma brucei*, transmitted by hematophagous tsetse flies. African populations have developed specific genetic mechanisms to control the disease. The role of various cytokine molecules has been demonstrated (Ilboudo et al., 2014). The haptoglobin-related protein (HPR) is found in a CNV region that exhibits a higher copy number in the Yoruba individuals (of African ancestry) than in the individuals of Asian and European ancestry. This pattern could be related to adaptation to HAT. The linked SNPs also show high *F*st values (= differentiation) among populations of different ancestries (Armengol et al., 2009). AFAs suffer from kidney disease—including focal segmental glomerulosclerosis (FSGS) and hypertension-attributed end-stage kidney disease (H-ESKD)—at higher rates than EURAs. Two independent coding variants of the Apolipoprotein L1 (*APOL1*) gene are strongly associated with FSGS and H-ESKD. It has been suggested that these variants were involved in resistance against *T. brucei* (Karlsson et al., 2014; Lachance and Tishkoff, 2013; Sudmant et al., 2015). Passed adaptation to HAT is therefore hypothesized to be at the origin of the present kidney disease burden in AFAs.

Other Transmissible Diseases

Visceral leishmaniosis (caused by the parasitic protozoan *Leishmania infantum*) shows strong ethnic differences in the ratio of asymptomatic to symptomatic infections (Bucheton et al., 2002). The GWAS involved in tuberculosis show that accurate identification of populations is indispensable for ruling out the misleading impact of stratification. The GWAS conducted on Gambians and Ghanaians reported an 8% imputation error rate when using the Nigerian Yoruban reference population (Chapman and Hill, 2012). Among the various polymorphisms having undergone recent evolution (and therefore likely to be geographically restricted) identified by Grossman et al. (2013) were genes related to infection by *Yiersinia pestis*, the agent of plague, *Mycobacterium leprae*, which causes leprosy, *Mycobacterium tuberculosis*, *Salmonella typhimurium*, the agent of typhoid fever, Lassa virus, and measles virus. Heyn et al. (2013) evidenced differential methylation (related to gene regulation), among distinct human groups, in genes related to the different penetrance rates of infection by enteropathogenic *Escherichia coli*, measles virus, and hepatitis B virus. The genes involved in leprosy resistance are not the same in Indian and Chinese populations (Karlsson et al., 2014). In Brazil, some genes are potential markers for susceptibility to leprosy development, while others are potential markers for the severe clinical multibacillary (MB) form (Pinto et al., 2015). These markers are influenced by ancestry. European admixture increases the risk of leprosy development, while African admixture is protective against leprosy (Pinto et al., 2015). Smallpox resistance seems to have been selected in African populations. In AFAs, the cytokine response to smallpox vaccination is stronger than in EURAs, which supports a larger effect due to selection in Africa (Karlsson et al., 2014). Hepatitis C susceptibility differs among human geographical groups, due to HLA variation (Thio et al., 2001). A hepatitis C-protective C allele of the Interleukin 28B (*IL28B*) gene is most prevalent in Asians, has an intermediary frequency in Europeans, and has its lowest prevalence in Africans. The higher frequency in non-African populations may be the result of positive selection (Manry and Quintana-Murci, 2013).

Different Human Populations Carry Different Pathogen Strains

The genetic evolution of the *Helicobacter pylori* bacterium (which causes gastric ulcers) is related to the evolution of

human populations since the advent of modern humans. Different human populations harbor distinct genotypes of the bacterium (Moodley et al., 2012). Hirsh et al. (2004) showed that strains of *M. tuberculosis* (the bacterium responsible for tuberculosis) isolated from patients of different ancestry groups in San Francisco reflected the genetic polymorphism of the strains of their country of origin. These authors evidenced a Southeast Asian cluster, a Filipino cluster, and two clusters having the dominant North American *M. tuberculosis* type. Lastly, in admixed Colombian populations characterized by AIMs, the genotypes of *M. leprae* (the bacterium responsible for leprosy) are correlated with the degree of either African or European ancestry (Cardona-Castro et al., 2015).

Impact of Human Behavior on Infectious Disease Transmission: The Niche Construction Theory and the Baldwin Effect

The niche construction theory (Laland et al., 2010) states that, by modifying their environments, organisms influence the natural selection acting on themselves. In tropical areas, sweet potato farming increased the density of water pools, which favored the proliferation of anopheline mosquito larvae and the spread of malaria. This is assumed to have increased selection for malaria genetic resistance (Cochran and Harpending, 2009, Chapter 4; Laland et al., 2010). The same probably occurred in Southeast Asia with rice farming and all diseases transmitted by mosquitoes. In Egypt, the construction of the Aswan dam, with its huge reservoir, favored the transmission of schistosomiasis, a disease brought on by a worm whose larvae are transmitted by freshwater snails. In contrast, sanitation of the Pontine marshes in Italy before the Second World War interrupted the transmission of malaria in the Rome area. Every time men modify their environment, they influence the transmission and hence the selective pressure of infectious diseases. The Baldwin effect postulates the impact on natural selection of learned behavior through cultural transmission. Richerson et al. (2010) proposed that its impact on human biological evolution was considerable. Obviously, newly acquired behavior may play an important role on infectious disease transmission. For example, medical education in tropical Africa seeks to change the habit of keeping used tires in one's garden. Tires fill with rainwater and become a mosquito larva nursery. Both niche construction and the Baldwin effect act unevenly on different geographical populations having different cultures and behaviors and will therefore have dissimilar impacts on the natural selection caused by pathogens.

INFLAMMATORY AND AUTOIMMUNE DISEASES: THE HYGIENE HYPOTHESIS

The hygiene hypothesis (Sironi and Clerici, 2010) states that the human immune system has been selected to face a considerable pathogen pressure. In modern societies, this pressure is relaxed. As a result, the immune system runs on empty and "overspeeds," leading to allergic, inflammatory, and autoimmune diseases. The forces related to the hygiene hypothesis are obviously stronger in industrialized countries, which should lead to an uneven distribution of these diseases throughout the world.

As a matter of fact, autoimmune diseases such as alopecia areata, membranous nephropathy, primary biliary cirrhosis, systemic lupus erythematosus, systemic sclerosis, ulcerative colitis, and vitiligo underwent genetic risk differentiation in 51 populations of the Human Genome Diversity panel surveyed by Corona et al. (2013). Fumagalli et al. (2011) found that the diversity of the local pathogen environment was the predominant driver of local adaptation. They looked for loci targeted by pathogen-driven local selection, and found an enrichment of genes associated with autoimmune diseases, such as celiac disease, Crohn's disease, type 1 diabetes, and multiple sclerosis.

Asthma is an inflammatory respiratory disease. As we have seen above in "Respiratory diseases," it has an uneven distribution among people of different ancestries. Asthma could be caused by an inappropriate response of the immune system in modern, hygienically cleaned environments (Richerson et al., 2010). Crohn's disease is almost exclusively found in people of European ancestry (Mountain and Risch, 2004). The autoimmune skin disease pemphigus vulgaris has a high frequency in AJs (Guha et al., 2012). Multiple sclerosis is the most common autoimmune disorder affecting the central nervous system. It is more frequent in Northern Europeans (Compston and Coles, 2008). Migrant studies have shown that the frequency of multiple sclerosis remains lower in Canadian Asians than in Canadian Europeans (Risch et al., 2002), which suggests that genetics plays a stronger role than the environment as a cause of this disease.

The GWAS of autoimmune diseases revealed extensive overlap in genetic variants linked to a diverse range of disorders, including celiac disease, Crohn's disease, multiple sclerosis, psoriasis, rheumatoid arthritis, systemic lupus erythematosus, and type 1 diabetes (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). This suggests a common selective pressure (hygiene hypothesis?) for these clinically diversified disorders. The range of diseases affected by ancient pathogen pressure actually extends beyond infectious and autoimmune diseases, since inflammatory and immunity genes are also

associated with mental disorders, including SCZ and autism (Karlsson et al., 2014).

RESISTANCE ALLELES

At the end of this world tour of disease genes, it should be noted that the search for disease genes has been more widely undertaken in people of European ancestry than in other groups. There is now a tendency to emphasize large multiethnic WGS surveys to encourage filling this gap (Harper et al., 2015). Moreover, until now, researchers have looked more for disease genes than for disease resistance genes. This research theme now appears to be fast-developing and promising, especially in the perspective of improved drug development. Protective alleles often function by loss of function (LoF), by attenuating a genic activity. Regulatory phenomena are important in modulating their action. These protective alleles often are RVs and sometimes are specific of given ancestry groups. A strategy to look for them is to compare disease distribution among ancestry groups. If a given disease has a high prevalence in a given group, it is inferred that the other groups have protective alleles (Harper et al., 2015).

CONCLUDING REMARKS

The wealth of data yielded by modern genomics has considerably clarified our view on the genetic background of many diseases. It has confirmed that Mendelian, monogenic diseases tend to be geographically restricted.

When complex diseases are considered, this geographical uneven distribution is verified in many cases, which is probably the result of local adaptation to specific selective pressures. More and more genetic variants involved in complex diseases are coming to light, including in psychological disorders. This will make it possible to partition the respective impact of the environment and the genetic background, and the interactions between the two, in the etiology of these diseases. However, this research is made difficult by the fact that many complex disorders are caused by RVs, requiring that vast population samples be surveyed.

As for infectious diseases and autoimmune disorders, geographical differentiation is especially clear, since pathogen and vector pressures are highly dependent upon climatic conditions, and hygiene measures have dramatically impacted different situations in countries with different cultures and economic levels.

Uneven geographical repartition of many diseases does not imply that they are totally absent in some geographical populations. The concern that the notion of a higher frequency of some diseases (cystic fibrosis, hemoglobinopathies) in certain populations could lead to misdiagnoses (Yudell et al., 2016) is unfounded. Any physician is aware that ancestry may give higher probabilities of diagnosis in some cases, but not certainty.

The new research on protective alleles shows that these protective variants are often rare and sometimes are ancestry-group specific.

Lastly, genetic heterogeneity within major continental groups (structuration) and admixture should be carefully taken into account in the study of disease genetics.

The complex interplay between genes, culture, environment, and socioeconomic factors in the etiology and severity of diseases calls for extensive multidisciplinary collaborations among specialists in the biological, medical, and social sciences. This need is reflected in the design of the present book.

GLOSSARY

Cytokine An intercellular messenger protein that is released by lymphocytes and macrophages. Cytokines favor communication among cells of the immune system and between immune system cells and cells belonging to other tissue categories. They play an important role in the defense against infectious agents.

Human leukocyte antigens (HLA) Cell-surface proteins detected by blood tests that exhibit huge diversity among humans and determine an individual's leukocyte type. The HLA set of genes is involved in the presentation of antigenic peptides to the immune system and plays a major role in tissue compatibility and infectious processes.

Linkage disequilibrium nonrandom association of genotypes occurring at different loci.

Major histocompatibility complex (MHC) A complex of genes found in mammals (HLA in humans) that function in determining the histocompatibility antigens found on cell surfaces.

REFERENCES

Abel, L., Dessein, A.J., 1997. The impact of host genetics on susceptibility to human infectious diseases. Current Opinion in Immunology 9, 509–516.

Allison, A.C., 1956. The sickle-cell and haemoglobin C genes in some African populations. Annals of Human Genetics 21, 67–89.

Armengol, L., Villatoro, S., González, J.R., et al., 2009. Identification of copy number variants defining genomic differences among major human groups. PLoS One e7230. http://dx.doi.org/10.1371/journal.pone.0007230.

Avise, J.C., 2004. Molecular Markers, Natural History and Evolution, second ed. Chapman & Hall, New York London.

Ayala, F.J., Escalante, A., 1996. The evolution of human populations: a molecular perspective. Molecular Phylogenetics and Evolution 5, 188–201.

Ayub, Q., Yngvadottir, B., Chen, Y., Xue, Y., Hu, M., Vernes, S.C., Fisher, S.E., Tyler-Smith, C., 2013. FOXP2 targets show evidence of positive selection in European populations. The American Journal of Human Genetics 92, 696–706.

Barbujani, G., Colonna, V., 2010. Human genome diversity: frequently asked question. Trends in Genetics 26, 285–295.

Belizário, J.E., 2013. The humankind genome: from genetic diversity to the origin of human diseases. Genome 56, 705–716.

Betancourt, H., López, S.R., 1993. The study of culture, ethnicity, and race in American Psychology. American Psychologist 48, 629–637.

Birky, C.W., 2009. *Giardia* sex? Yes, but how and how much? Trends in Parasitology 26, 70–74.

Blackwell, J.M., 1996. Genetic susceptibility to Leishmanial infections: studies in mice and man. Parasitology 112 (Suppl.), S67–S74.

Bucheton, B., Kheir, M.M., El-Safi, S.H., et al., 2002. The interplay between environmental and host factors during an outbreak of visceral leishmaniasis in eastern Sudan. Microbes and Infection 4, 1449–1457.

Burchard, E.G., Oh, S.S., Foreman, M.G., Celedón, J.C., 2015. Moving toward true inclusion of racial/ethnic minorities in federally funded studies. A key step for achieving respiratory health equality in the United States. American Journal of Respiratory and Critical Care Medicine 191, 514–521.

Burdick, K.E., Lencz, T., Funke, B., et al., 2006. Genetic variation in DTNBP1 influences general cognitive ability. Human Molecular Genetics 15, 1563–1568.

Bustamante, C.D., González Burchard, E., De La Vega, F.M., 2011. Genomics for the world. Nature 475, 163–165.

Cardona-Castro, N., Cortés, E., Beltrán, C., et al., 2015. Human genetic ancestral composition correlates with the origin of *Mycobacterium leprae* strains in a leprosy endemic population. PLoS Neglected Tropical Diseases 9 (9), e0004045. http://dx.doi.org/10.1371/journal.pntd.0004045.

Cavalli-Sforza, L., 2007. Human evolution and its relevance for scientific epidemiology. Annual Review of Genomics and Human Genetics 8, 1–15.

Chapman, S.J., Hill, A.V.S., 2012. Human genetic susceptibility to infectious disease. Nature Reviews Genetics 13, 175–188.

Cochran, G., Harpending, H., 2009. The 10,000 Year Explosion- How Civilization Accelerated Human Evolution. Basic Books. A Member of the Perseus Books Group, New York.

Cochran, G., Hardy, J., Harpending, H., 2006. Natural history of ashkenazi intelligence. Journal of Biosocial Science 38, 659–693.

Colonna, V., Ayub, Q., Chen, Y., et al., 2014. Human genomic regions with exceptionally high levels of population differentiation identified from 911 whole-genome sequences. Genome Biology 15, R88.

Compston, A., Coles, A., 2008. Multiple sclerosis. Lancet 372 (9648), 1502–1517.

Conrad, D.F., Hurles, M.E., 2007. The population genetics of structural variation. Nature Genetics 39 (Suppl.), 530–536.

Corona, E., Chen, R., Sikora, M., et al., 2013. Analysis of the genetic basis of disease in the context of worldwide human relationships and migration. PLoS Genetics 9 (5), e1003447. http://dx.doi.org/10.1371/journal.pgen.1003447.

Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Lancet 381, 1371–1379.

Daub, J.T., Hofer, T., Cutivet, E., et al., 2013. Evidence for polygenic adaptation to pathogens in the human genome. Molecular Biology and Evolution 30, 1544–1558.

de Candia, T.R., Hong Lee, S., Yang, J., et al., 2013. Additive genetic variation in schizophrenia risk is shared by populations of African and European descent. The American Journal of Human Genetics 93, 463–470.

Dean, M., Carrington, M., Winckler, C., et al., 1996. Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CKR5 structural gene. Science 273, 1856–1862.

Farrer, L.A., Cupples, L.A., Haines, J.L., et al., 1997. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA 278, 1349–1356.

Fisher, R.A., 1918. The correlations between relatives on the supposition of Mendelian inheritance. Philosophical Transactions of the Royal Society of Edinburgh 52, 399–433.

Frances, A., 2013. Saving Normal: An Insider's Revolt Against Out-of-control Psychiatric Diagnosis, -5, Big Pharma, and the Medicalization of Ordinary Life. William Morrow, New York.

Fraser, H.B., 2013. Gene expression drives local adaptation in humans. Genome Research 23, 1089–1096.

Fu, W., Akey, J.M., 2013. Selection and adaptation in the human genome. Annual Review of Genomics and Human Genetics 14, 467–489.

Fu, W., O'Connor, T.D., Jun, G., et al., 2013. Analysis of 6515 exomes reveals the recent origin of most human protein-coding variants. Nature 493, 216–220.

Fumagalli, M., Sironi, M., Pozzoli, U., et al., 2011. Signatures of environmental genetic adaptation pinpoint pathogens as the main selective pressure through human evolution. PLoS Genetics 7 (11), e1002355. http://dx.doi.org/10.1371/journal.pgen.1002355.

Gentillini, M., Caumes, E., Danis, M., et al., 2012. Médecine Tropicale, 6e éd. Lavoisier, Paris.

Geschwind, D.H., Flint, J., 2015. Genetics and genomics of psychiatric disease. Science 349, 1489–1494.

Gonzaga-Jauregui, C., Lupski, J.R., Gibbs, R.A., 2012. Human genome sequencing in health and disease. Annual Review of Medicine 63, 35–61.

González Burchard, E., Ziv, E., Coyle, N., et al., 2003. The importance of race and ethnic background in biomedical research and clinical practice. The New England Journal of Medicine 348, 1170–1175.

Gonzalez, E., Kulkarni, H., Bolivar, H., et al., 2005. The influence of *CCL3L1* gene-containing segmental duplications on HIV-1/AIDS susceptibility. Science 307, 1434–1440.

Grossman, S.R., Andersen, K.G., Shlyakhter, I., et al., 2013. Identifying recent adaptations in large-scale genomic data. Cell 152, 703–713.

Guha, S., Rosenfeld, J.A., Malhotra, A.K., et al., 2012. Implications for health and disease in the genetic signature of the Ashkenazi Jewish population. Genome Biology 13, R2.

Gurdasani, D., Carstensen, T., Tekola-Ayele, F., et al., 2015. The African genome variation project shapes medical genetics in Africa. Nature 517, 327–332.

Haldane, J.B.S., 1949. Disease and evolution. La ricerca scientifica Suppl. 19, 68–76.

Hardelid, P., Cortina-Borja, M., Munro, A., et al., 2008. The birth prevalence of PKU in populations of European, South Asian and Sub-Saharan African ancestry living in South East England. Annals of Human Genetics 72, 65–71.

Harper, A.R., Nayee, S., Topol, E.J., 2015. Protective alleles and modifier variants in human health and disease. Nature Reviews Genetics 16, 689–701.

Harris, K.M., Edlund, M.J., Larson, S., 2005. Racial and ethnic differences in the mental health problems and use of mental health care. Medical Care 43, 775–784.

Harris, K., 2015. Evidence for recent, population-specific evolution of the human mutation rate. Proceedings of the National Academy of Sciences of the United States of America 112, 3439–3444.

Helgadottir, A., Manolescu, A., Helgason, A., et al., 2006. A variant of the gene encoding leukotriene A4 hydrolase confers ethnicity-specific risk of myocardial infarction. Nature Genetics 38, 68–74.

Heyn, H., Moran, S., Hernando-Herraez, I., et al., 2013. DNA methylation contributes to natural human variation. Genome Research 23, 1363–1372.

Hirsh, A.E., Tsolaki, A.G., DeRiemer, K., Feldman, M.W., Small, P.M., 2004. Stable association between strains of *Mycobacterium tuberculosis* and their human host populations. Proceedings of the National Academy of Sciences of the United States of America 101, 4871–4876.

Hyman, S., 2014. Depression needs large human-genetics studies. Nature 515, 189–191.

Ilboudo, H., Bras-Gonçalves, R., Camara, M., et al., 2014. Unravelling human trypanotolerance: IL8 is associated with infection control whereas IL10 and TNFα are associated with subsequent disease development. PLoS Pathogens 10 (11), e1004469. http://dx.doi.org/10.1371/journal.ppat.1004469.

Jordan, B., 2008. L'humanité au pluriel. La génétique et la question des races. Editions du Seuil, Paris.

Jorde, L.B., Wooding, S.P., 2004. Genetic variation, classification and "race". Nature Genetics 36 (Suppl.), S28–S32.

Karlsson, E.K., Kwiatkowski, D.P., Sabeti, P.C., 2014. Natural selection and infectious disease in human populations. Nature Reviews Genetics 15, 379–383.

Keita, S.O.Y., Kittles, R.A., Royal, C.D.M., et al., 2004. Conceptualizing human variation. Nature Genetics 36 (Suppl.), S17–S20.

Lachance, J., Tishkoff, S.A., 2013. Population genomics of human adaptation. Annual Review of Ecology, Evolution, and Systematics 44, 123–143.

Laland, K.N., Odling-Smee, J., Myles, S., 2010. How culture shaped the human genome: bringing genetics and the human sciences together. Nature Reviews Genetics 11, 137–148.

Lander, E.S., 2011. Initial impact of the sequencing of the human genome. Nature 470, 187–197.

Lee, S.S., Mudaliar, A., 2009. Racing forwards: the genomics and personalized medicine act. Science 323, 342.

Lee, S.S., Mountain, J., Koenig, B., et al., 2008. The ethics of characterizing difference: guiding principles on using racial categories in human genetics. Genome Biology 9, 404. http://dx.doi.org/10.1186/gb-2008-9-7-404.

Li, J.Z., Absher, D.M., Tang, H., et al., 2008. Worldwide human relationships inferred from genome-wide patterns of variation. Science 319, 1100–1104.

López Herráez, D., Bauchet, M., Tang, K., et al., 2009. Genetic variation and recent positive selection in worldwide human populations: evidence from nearly 1 million SNPs. Plos One 4 (11), e7888. http://dx.doi.org/10.1371/journal.pone.0007888.

Manry, J., Quintana-Murci, L., 2013. A genome-wide perspective of human diversity and its implications in infectious disease. Cold Spring Harbor Perspectives in Medicine 3, a012450.

Mersha, T.B., Abebe, T., 2015. Self-reported race/ethnicity in the age of genomic research: its potential impact on understanding health disparities. Human Genomics. http://dx.doi.org/10.1186/s40246-014-0023-x.

Miller, L.H., 1994. Impact of malaria on genetic polymorphism and genetic diseases in Africans and African Americans. Proceedings of the National Academy of Sciences United States of America 91, 2415–2419.

Modiano, D., Chiucchiuini, A., Petrarca, V., et al., 1999. Interethnic differences in the humoral response to non-repetitive regions of the *Plasmodium falciparum* circumsporozoite protein. American Journal of Tropical Medicine and Hygiene 61, 663–667.

Moodley, Y., Linz, B., Bond, R.P., et al., 2012. Age of the association between *Helicobacter pylori* and man. PLoS Pathogens 8 (5), e1002693. http://dx.doi.org/10.1371/journal.ppat.1002693.

Moreno-Estrada, A., Gignoux, C.R., Fernández-López, J.C., et al., 2014. The genetics of Mexico recapitulates Native American substructure and affects biomedical traits. Science 344, 1280–1285.

Mountain, J.L., Risch, N., 2004. Assessing genetic contribution to phenotypic differences among "racial" and "ethnic" groups. Nature Genetics 36 (Suppl.), S48–S53.

Need, A.C., Kasperavičiūtė, D., Cirulli, E.T., Goldstein, D.B., 2009. A genome-wide genetic signature of Jewish ancestry perfectly separates individuals with and without full Jewish ancestry in a large random sample of European Americans. Genome Biology 10, R7.

Neel, J., 1962. Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? The American Journal of Human Genetics 14, 353–362.

Nei, M., 1978. The theory of genetic distance and evolution of human races. Japanese Journal of Human Genetics 23, 341–369.

Ostrer, H., Skorecki, K., 2013. The population genetics of the Jewish people. Human Genetics 132, 119–127.

Pickrell, J.K., Coop, G., Novembre, J., et al., 2009. Signals of recent positive selection in a worldwide sample of human populations. Genome Research 19, 826–837.

Pinto, P., Salgado, C., Pereira Carneiro Santos, N., Santos, S., Ribeiro-dos-Santos, A., 2015. Influence of genetic ancestry on INDEL markers of NFKβ1, CASP8, PAR1, IL4 and CYP19A1 genes in leprosy patients. PLoS Neglected Tropical Diseases 9 (9), e0004050. http://dx.doi.org/10.1371/journal.pntd.0004050.

Prugnolle, F., Manica, A., Charpentier, M., et al., 2005. Pathogen-driven selection and worldwide HLA class I diversity. Current Biology 15, 1022–1027.

Racimo, F., Sankararaman, S., Nielsen, R., Huerta-Sánchez, E., 2015. Evidence for archaic adaptive introgression in humans. Nature Reviews Genetics 16, 359–371.

Richerson, P.J., Boyd, R., Henrich, J., 2010. Gene-culture coevolution in the age of genomics. Proceedings of the National Academy of Sciences of the United States of America 107 (Suppl. 2), 8985–8992.

Risch, N., Burchard, E., Ziv, E., Tang, H., 2002. Categorization of humans in biomedical research: genes, race and disease. Genome Biology 3 (7) comment2007.1–comment2007.12.

Rosenberg, N.A., Mahajan, S., Ramachandran, S., et al., 2005. Clines, clusters, and the effect of study design on the inference of human population structure. PLoS Genetics 1 (6), e70.

Sarich, V., Miele, F., 2004. Race: The Reality of Human Differences. Westview Press, Boulder, Colorado, USA.

Shendure, J., Akey, J.M., 2015. The origins, determinants, and consequences of human mutations. Science 345, 1478–1483.

Sironi, M., Clerici, M., 2010. The hygiene hypothesis: an evolutionary perspective. Microbes and Infection 12, 421–427.

Spielman, R.S., Bastone, L.A., Burdick, J.T., et al., 2007. Common genetic variants account for differences in gene expression among ethnic groups. Nature Genetics 39, 226–231.

Sudmant, P.H., Mallick, S., Nelson, B.J., et al., 2015. Global diversity, population stratification, and selection of human copy-number variation. Science. http://dx.doi.org/10.1126/science.aab3761.

Tanner, M.J., Bruce, L., Martin, P.G., Rearden, D.M., Jones, G.L., 1991. Melanesian hereditary ovalocytes have a deletion in red cell band 3. Blood 78, 2785−2786.

Tate, S.K., Goldstein, D.B., 2004. Will tomorrow's medicine work for everyone? Nature Genetics 36 (Suppl.), S34−S42.

Tennessen, J.A., Bigham, A.W., O'Connor, T.D., et al., 2012. Evolution and functional impact of rare coding variation from deep sequencing of human exomes. Science 337, 64−69.

The 1000 Genomes Project Consortium, 2012. An integrated map of genetic variation from 1,092 human genomes. Nature 491, 56−65.

Thio, C.L., Thomas, D.L., Goedert, J.J., et al., 2001. Racial differences in HLA class ii associations with hepatitis C virus outcomes. Journal of Infectious Diseases 184, 16−21.

Tibayrenc, M., Ayala, F.J., 2013. How clonal are *trypanosoma* and *Leishmania*? Trends in Parasitology 29, 264−269.

Tibayrenc, M., 1998. Genetic epidemiology of parasitic protozoa and other infectious agents: the need for an integrated approach. International Journal for Parasitology 28 (1), 85−104.

Tibayrenc, M., 2004. The impact of human genetic diversity in the transmission and severity of infectious diseases. In: Dronamraju, K. (Ed.), Infectious Disease: Host-pathogen Evolution. Cambridge University Press, pp. 315−324.

Tibayrenc, M., 2007a. Human genetic diversity and epidemiology of parasitic and other transmissible diseases. Advances in Parasitology 64, 378−428.

Tibayrenc, M., 2007b. Human genetic diversity and the spread of infectious diseases. In: Tibayrenc, M. (Ed.), Encyclopedia of Infectious Diseases: Modern Methodologies. Wiley & Sons, pp. 321−335.

Tishkoff, S.A., Kidd, K.K., 2004. Implications of biogeography of human populations for "race" and medicine. Nature Genetics 36 (Suppl.), S21−S27.

Tishkoff, S., 2015. Strength in small numbers. Science 349, 1282−1283.

Van Valen, L., 1973. A new evolutionary law. Evolutionary Theory 1, 1−30.

Vasseur, E., Quintana-Murci, L., 2013. The impact of natural selection on health and disease: uses of the population genetics approach in humans. Evolutionary Applications 6, 596−607.

Williams, D.R., González, H.M., Neighbors, H., et al., 2007. Prevalence and distribution of major depressive disorder in African Americans, Caribbean blacks, and non-Hispanic Whites. Results from the national survey of American life. Archives of General Psychiatry 64, 305−315.

Yudell, M., Roberts, D., DeSalle, R., Tishkoff, S., 2016. Taking race out of human genetics. Science 351, 564−565.

Zietsch, B.P., de Candia, T.R., Keller, M.C., 2015. Evolutionary behavioral genetics. Current Opinion in Behavioral Sciences 2, 73−80.

Chapter 11

Natural Selection Associated With Infectious Diseases

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INFECTIOUS DISEASES AND HUMAN EVOLUTION

Evolution of Anatomically Modern Humans

The earliest remains of anatomically modern humans (AMHs) were found in central East Africa and dated to around 150,000 years ago (White et al., 2003). It is believed AMHs greatly expanded the distribution range after the out-of-Africa (OOA) dispersal some 50,000 years ago (Pagani et al., 2015) eventually colonizing the vast majority of landmasses (Raghavan et al., 2015). During this migration, humans were exposed to new environments, including different climatic conditions and novel zoonotic pathogens, and had to adapt their diet to local food availability (Balaresque et al., 2007). Such exposure to new environments generated selective pressures that in turn led to genetic adaptations that are believed to have played an important role in human evolution (Harris and Meyer, 2006) and contributed to differentiation between human populations (Barreiro et al., 2008).

The ancient human migration to colder climates with less incident sunlight had adaptive consequences for pigmentation and metabolic traits (Hancock et al., 2011, 2008; Izagirre et al., 2006). Likewise, changes in the subsistence strategy (for instance, after the advent of agriculture) led to the establishment of larger and more connected social groups and to the availability of novel sources of food, with a notable impact on metabolism (Hardy et al., 2015). Finally, population expansion, recent human migrations, and colonization of new habitats enhanced the exposure to novel infective agents; the spread of such new diseases imposed selective pressures on the immune system (Fumagalli and Sironi, 2014), some of which left a detectable signature in the apportionment of genetic diversity in the human genome.

Several adaptations of human populations to novel environments led to phenotypes that are easy to characterize biochemically or even visually. Such examples include lower melanin pigmentation in populations living far from the equator due to reduced UV radiation (Alonso et al., 2008) and increased hemoglobin concentration in high altitude populations, such as Tibetans reflecting hypoxia at high altitude (Huerta-Sánchez et al., 2014; Yi et al., 2010). A spectacular example of genetic adaptation to diet is lactase persistence, where a mutation found at high frequency in Europeans, but essentially absent anywhere else, maintains the ability to degrade lactose through life which provides a selective advantage in populations practicing dairy farming (Gerbault, 2013).

Most genetic adaptations underpin phenotypes that are more difficult to characterize. This is true in particular for genetic adaptations providing resistance to infectious diseases. In such cases, the best guess is to identify signatures in the human genome that are characteristic of past natural selection rather than the traditional approach of linking genetic variants with phenotypes. Interestingly, many biological pathways involved in the regulation of the immune system, and in particular susceptibility to infectious diseases, are enriched with signatures of non-neutral evolution, likely reflecting past genetic adaptation to pathogen exposure (Barreiro and Quintana-Murci, 2010).

Human and Pathogens Coevolution

Infectious agents have exerted strong selective pressure on human populations as they represented the main cause of

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00011-9

death until recently. Despite medical progress, global selective pressure imposed by pathogens remains high today, with infectious diseases still representing one of the major causes of mortality.

In addition to the pressure of constant exposure to endemic diseases, new infectious diseases emerge and wane and can have dramatic demographic impacts on the populations affected. Examples include the Black Death, which killed nearly half of the human population in Europe in the Middle Ages (Benedictow, 2004), or the exposure of indigenous populations from Central and South America to novel diseases such as smallpox and typhus after the arrival of Europeans during the 15th and 16th centuries (Waldman, 2009). Despite all the medical progress in recent decades, pandemics of novel infectious agents still occur. One example of an ongoing pandemic is HIV, which entered the human population around 1920 and has led to around 75 million cases so far (Faria et al., 2014).

Throughout their evolutionary history, humans have been exposed to a wide and varying array of pathogens. Like all other living organisms, humans have had a direct effect on the fitness of all organisms they interact with and have had to constantly adapt to cope with a wide range of pathogens. This need for constant adaptation of hosts and pathogens is often referred as an arms race, or the red queen hypothesis (Williams, 1975), as an analogy with Lewis Carroll's Red Queen, where both Alice and the Red Queen have to run just to stay in place.

DETECTING NATURAL SELECTION IN THE HUMAN GENOME

Forms of Natural Selection

Natural selection is the process whereby a heritable trait that increases the fitness of its carrier (ie, the organism's chance to survive and reproduce) becomes more common over time, as it is more likely to be passed on to offspring. While mutations arise (essentially) at random in the genome, their fate (change in frequency) is a function of their effect on the carrier's phenotype. Different forms of natural selection alter the change in frequency of the functional allele in different ways (Nielsen, 2005). Different forms of natural selection have been both characterized from a theoretical perspective and described in nature.

Selection may lead to an increase in the frequency of a beneficial allele (positive selection) until all individuals will carry such advantageous allele, a process which is referred to as fixation of the allele in the population. Negative selection will instead tend to reduce the frequency of deleterious mutations and eventually remove them from the pool of individuals. As new mutations are more likely to be either neutral or deleterious than beneficial, negative selection is the most widespread form of selection (Nielsen, 2005). Background selection refers to the continuous removal of new deleterious alleles in the human genome.

In some cases, the individual's phenotype is the result of the interaction between multiple alleles at a site. Balancing selection is the selective process that maintains high levels of genetic variation at a particular locus by keeping all beneficial alleles at common frequency in the population (Charlesworth, 2006). Typical examples of balancing selection are heterozygote advantage (or overdominance, where heterozygous individuals have a higher fitness than homozygotes) and frequency-dependent selection (where common alleles are maintained in a context of equilibrium in communities).

Historically, positive selection has attracted considerable attention among researchers. One reason for this is that adaptation (the observation that particular phenotypes are advantageous in a specific environment) is thought to be primarily driven by positive selection. Positive selection also leaves clear and peculiar genomic footprints, while other forms of selection may lead to uninformative or cryptic distortions of genetic variation.

The identification of mutations under natural selection in the human genome has a twofold meaning. Firstly, these loci are informative on which selective events have shaped genome diversity, and allow gaining insight on past evolutionary events that characterized human history. Secondly, since natural selection acts only on sites that affect the phenotype, alleles targeted by selection are likely to be of biological and functional relevance. For instance, alleles highlighted in studies aiming at identifying signals of natural selection are often associated with resistance to infectious diseases (Karlsson et al., 2014), which is in line with the hypothesis that pathogens have exerted some of the strongest selective pressures during human evolution.

Methods to Detect Signatures of Natural Selection

Different forms of selection leave distinct molecular signatures at the local genomic level, such as variation in polymorphism levels, allele frequencies, haplotype diversity, and population differentiation (Nielsen, 2005). Various statistical approaches to identify genomic regions targeted by natural selection have been devised. These methods differ in the type of selection they are aiming to detect and exhibit different power depending on selection timing and strength. Nevertheless, the main rationale is similar overall, as these strategies compute summary statistics to compare the observed local genetic variation with expectations under the null hypothesis of neutral evolution.

The first class of methods ever developed to detect selection in the human genome is based on the comparison of orthologous genes among primate species. These approaches are useful to detect positive selection acting over long evolutionary timescales, which created phenotypic changes between species (Kosiol et al., 2008). By identifying homologous sequences that show low variation among species (ie, evolutionary conserved), it is possible to identify functional loci, such as coding regions or shared regulatory elements among related taxa. Conversely, one can potentially identify genomic regions that exhibit accumulation of substitutions in particular branches, and thus lineage-specific accelerations in the rate of evolution suggestive of strong positive selection having affected some of the lineages (Pollard et al., 2010).

In this context, the most-commonly used statistic for detecting selection is d_N/d_S which computes the ratio between nonsynonymous substitutions rate and the synonymous substitutions rate (Yang and Bielawski, 2000). The idea underlying this statistic is that synonymous changes (which do not affect the protein sequence) are more likely to be functionally neutral, while nonsynonymous changes also alter the amino acid sequence and thus potentially the individual's phenotype. Under these assumptions, the action of positive selection may result in an excess of nonsynonymous substitutions, as novel protein structures are beneficial. A d_N/d_S value greater than 1 is suggestive of positive selection acting on the locus under scrutiny. On the contrary, negative selection will tend to decrease the nonsynonymous changes rate and d_N/d_S value will fall below 1.

Since the availability of multiple genomes from human populations, richer statistics have been proposed. For instance, the McDonald-Kreitman (MK) test extends d_N/d_S statistic by incorporating intraspecific diversity (McDonald and Kreitman, 1991; Messer and Petrov, 2013). If the between-species d_N/d_S value is greater than the within-species d_N/d_S value, then positive selection acting on differentiating the two species might have created such a scenario. Using a similar rationale, the Hudson-Kreitman-Aguade (HKA) method tests whether a particular locus or gene exhibits an excess or deficiency of polymorphism levels compared to the baseline replacement rate, with the assumption that positive selection in one species causes a relative reduction of polymorphisms compared to fixed differences (Hudson et al., 1987; Wright and Charlesworth, 2004).

Comparative genomics studies therefore focus on elements, which tend to be conserved in most of the species analyzed but show a significantly accelerated rate of substitution in a particular lineage. In genetic regions under strong background selection, mutations are quickly removed from the gene pool, resulting in highly conserved stretches of the genome (ie, regions where variation is not observed). This approach has been used to identify several hundred human-specific and primate-specific regions (Lindblad-Toh et al., 2011).

A second class of methods to detect selection signatures compares genetic variation within and between human populations. These methods are designed to highlight recent adaptive events. Rapid events of positive selection may result in a distortion of the allele frequency distribution in proximity of the beneficial allele arising in frequency, creating nucleotide diversity reduction within a genomic region surrounding a locus which has been affected by recent positive selection (selective sweep) (Kim and Nielsen, 2004). Such localized decay of genetic diversity, usually associated with increased homozygosity, has been exploited by several approaches aiming at detecting selection signatures in human populations (Nielsen et al., 2005; Pavlidis et al., 2013; Williamson et al., 2007).

The site frequency spectrum (SFS) records the proportion of sites with a certain sample allele frequency. As an illustration, assuming that the sample comprises N diploids individuals and for each single nucleotide polymorphism (SNP) we could assign the ancestral and derived allelic states, the unfolded SFS is described by $2N+1$ proportions of sites with derived allele frequency (DAF) from 0 to $2N$. While the whole-genome SFS is informative on the demographic history of the examined population, the local SFS is affected by nonneutral factors as well (if any). Positive and negative selection will produce an excess of rare variants, with a selective sweep specifically creating a higher proportion of high DAF sites than neutral expectations. An excess of intermediate frequency alleles is a hallmark of balancing selection. As an illustration, Fig. 11.1 depicts the expected SFS under neutrality, positive selection, and partial selective sweep with the beneficial mutation at 70% in frequency. Under selective regimes, high derived frequency variants are overrepresented compared to neutral expectations.

Several statistics have been proposed that quantify the distortion in the SFS due to selection. Tajima's D was the first, and for many years the most common test to detect such deviation; it compares the average pairwise nucleotide differences between individuals with the number of polymorphic sites (Tajima, 1989). Negative values of D suggest an overrepresentation of low-frequency variants (and thus positive selection), as they do not increase pairwise differences as much as intermediate-frequency variants. Positive values of D are an indication of an excess of intermediate-frequency variants that could be a signal of balancing selection. Several extensions of this metric have been proposed, either to account for the number of SNPs affecting internal or external branches of the gene tree, eg, Fu and Li's D and F

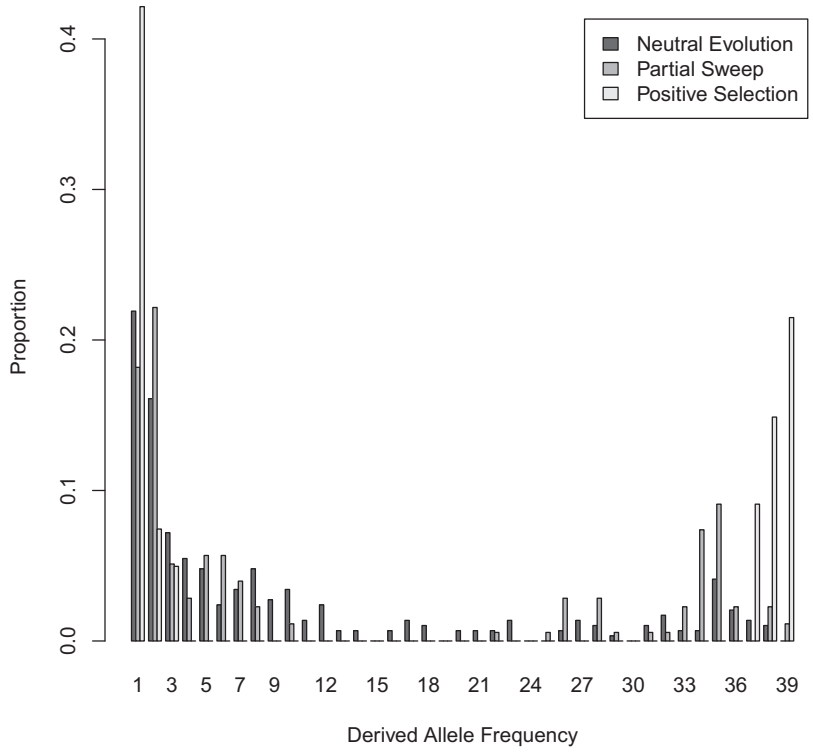

FIGURE 11.1 The effect of natural selection on the site frequency spectrum. The proportion of sites with distinct frequencies of the derived allele for 20 diploid individuals is recorded under different evolutionary histories. Outputs from single simulations under neutral evolution, positive selection (selection coefficient of 3%), or partial selective sweep (selection coefficient of 0.5% and current frequency of 70%) are shown. All simulations were run using a constant population size model.

statistics (Fu and Li, 1993), or to take into account an excess of high frequency derived alleles, eg, Fay and Wu's *H* statistic (Fay and Wu, 2000).

Along with an excess of intermediate-frequency alleles, balancing selection is characterized by other features, such as high polymorphism, divergent and common haplotypes, and a deep coalescent time, which could be further exploited to test for selection acting at the locus analyzed (Charlesworth, 2006). Additionally, long-term balancing selection may result in the maintenance of shared polymorphisms (also called trans-specific SNPs) if the same selection pressures acted prior to the time of speciation between the species under scrutiny (Cagliani et al., 2010; Gao et al., 2015). Local excess of polymorphism levels in the genome can be tested using a classical HKA test (Hudson et al., 1987) or via statistical modeling (Andrés et al., 2009; DeGiorgio et al., 2014).

When the beneficial allele increases in frequency due to selection, neighboring SNPs in linkage disequilibrium (LD) will also increase in frequency (Payseur and Nachman, 2002). The long haplotype formed at the end of the selective sweep will eventually be broken down by recombination events over time. Methods based on identifying extended regions in LD have power to detect signatures of recent positive selection, when the beneficial mutation has not reached fixation in the population yet. After fixation, mutation and recombination will blur the LD signal making the detection of the selective event more challenging. Tests based on LD measures are generally based on the calculation of the homozygosity for the extended haplotype starting from the putative causal variant, and highlight regions where the decay of such metrics across the genome is lower compared to neutral expectations (Tang et al., 2007; Voight et al., 2006; Zhang et al., 2006). Extreme values of extended homozygosity for long genomic distances are an indication of positive selection. Many genome-wide scans for selection have successfully identified putative nonneutrally evolving regions with a reduction of haplotype diversity and increased homozygosity (Grossman et al., 2013, 2010; Sabeti et al., 2007).

Presumably the most powerful approach to detect signatures of natural selection in the human genome is to compare the genetic variation between populations from distinct geographical areas. Human phenotypes are often distributed according to geographical gradients, as each trait value might be adapted to a particular environment. When one population is under a selective pressure, which is not present in another one, then the locus responsible for that specific adaptation will behave differently between

those populations. Specifically, its allele frequency might be remarkably different in distinct population, with the beneficial allele being at high frequency in regions where it confers an adaptive advantage, and low frequency where it behaves neutrally (Novembre and Di Rienzo, 2009). Tests based on detecting signals of population genetic differentiation as evidence of selection rely on this concept.

Historically, the most commonly used statistic to quantify population genetic differentiation is the fixation index (F_{ST}) (Weir and Hill, 2002; Wright, 1951), which computes the ratio between the genetic variance between populations and the total genetic variance (Reynolds et al., 1983). Large values of F_{ST} (up to 1) reflect extensive allelic (or haplotypic) differentiation between a pair of population, suggesting positive selection acting specifically on that locus in one of the two populations. One of the most striking examples of strong differentiation is the FY*O allele at the *DARC* gene, which leads to the absence of Fy antigen on red blood cells and protects against *P. vivax* infection. The allele is at or near fixation in most Sub-Saharan African populations but is very rare outside Africa leading to an F_{ST} close to unity, which is the highest recorded for any genetic markers in human populations (Cavalli-Sforza et al., 1994).

Conversely, small values of F_{ST} (down to 0) reflect a small degree of differentiation, either due to neutral, negative, or balancing selection. A number of variations from the original F_{ST} statistic have been proposed, generally based on statistical modeling of the allele frequency differentiation (Balding, 2003). By comparing allele frequencies in three populations, it is possible to understand in which population selection is specifically increasing the frequency of the beneficial allele. This is the rationale for the population branch statistic (PBS), which has been used, for instance, to detect selection in Tibetans by comparing allele frequencies against both Chinese and Europeans (Yi et al., 2010).

In cases where an allele confers a weak advantage to the carrier in a specific environment and such environment varies according to a cline across different geographical regions, it is expected to lead to a pattern of parallel variation between the frequency of the advantageous mutation and the environmental variable that acted as selective pressure (Hancock et al., 2010). This is the idea behind methods based on statistical correlations between population allele frequencies and environmental variables, as a strategy to identify patterns of local adaptation (Coop et al., 2010; Frichot et al., 2013; Raj et al., 2013). As an illustration, the genetic diversity of human genes of the major histocompatibility complex (MHC), human leukocyte antigens (HLA) Class I system, correlates with the number of endemic infectious diseases found in different parts of the world, possibly as a result of increased natural selection for diversity in the MHC genes in environments with higher diversity of pathogens (Prugnolle et al., 2005).

As each selection test captures a specific feature of the adaptive process, methods aiming at increasing the sensitivity of selection detection are based on combining the information from multiple statistics (Grossman et al., 2010). These approaches usually achieve a greater resolution at identifying the region, or even the specific variant, under selection.

An important factor to consider when assessing whether selection has been responsible for the establishment of a specific genomic pattern, is that neutral factors may lead to rejection of the hypothesis of neutral evolution. Demographic events can distort the patterns of genetic variation and mimic those expected under natural selection. For instance, a population expansion creates an excess of low frequency variants (compared to a constant evolving size population), a feature that could be interpreted as positive selection. Similarly, a population bottleneck produces a deficit of rare mutations in favor of common alleles, as expected under a balancing selection regime.

One way to circumvent this problem is based on the notion that while demography affects genetic diversity at the level of the whole genome, natural selection specifically acts on the frequency of single targeted sites or regions. Empirical strategies are often adopted by highlighting genes or SNPs that are outliers in the genome-wide distribution for a specific summary statistics. For instance, genes that show a degree of population genetic differentiation above the 99th percentile of the empirical distribution may be good candidates for genes under positive selection. In addition to this ranking based on their selection test statistics, enrichment for specific biological processes or molecular functions is usually performed to test whether selection is targeting a particular class of loci or domains.

Despite their widespread use, such empirical approaches are unable both to statistically test for selection and to estimate the fraction of the genome under positive selection (Kelley et al., 2006). A valid alternative would be to explicitly model human demographic history: the inclusion of demographic parameters, such as population size changes or migration rates, allows simulating genetic data that mimic the expectations under neutral evolution. Statistics computed for a gene are then compared to such simulated neutral distribution to assess statistical significance for the rejection of null hypothesis of no selection acting. This approach has become popular with recent progress in methods allowing to simulate large genetic data in a reasonably short computation time (Yuan et al., 2012). Moreover, several demographic models for human evolution have been proposed, enabling their use in the context of testing for positive selection at the level of the gene (Gutenkunst et al., 2009; Harris and Nielsen, 2013).

Classic cases of selective sweeps from de novo mutations have been shown to be less common than previously hypothesized (Hernandez et al., 2011). Instead, selection acting on preexisting mutations might be a more effective mechanism for genetic adaptation to novel environments (Pritchard et al., 2010). Positive selection on standing variation is more challenging to identify as its footprints depend on various parameters, such as the time of onset and initial allele frequency of the beneficial mutation (Wilson et al., 2014). Similarly, when multiple beneficial alleles rise in frequency, a scenario called soft sweeps, the unusual haplotype pattern generated does not lead to straightforward genomic signatures of natural selection (Garud et al., 2015; Garud and Rosenberg, 2015). Statistical methods based on simulating large-scale genetic data under a wide spectrum of evolutionary parameters may help unveiling such complex selection signatures (Peter et al., 2012).

Regardless of methodology, studies aiming at detecting signals of natural selection in the human genome share the ultimate goal of pinpointing functional variants to be prioritized for further in vitro/vivo experiments or targeted association studies (Grossman et al., 2013). Indeed, functional analyses are the only way to definitely identify the causal allele behind a phenotype of interest.

Resources Available: Data Sets and Bioinformatic Tools

Historically, the detection of signatures of natural selection has been hampered by the lack of extensive population genetic data. Limited sequencing data for few genes allowed the description of a handful of cases of adaptive evolution in the human genome (Akey, 2009). However, since the completion of the Human Genome Project in 2001 (Lander et al., 2001), our understanding of human genetic diversity has steadily increased. With the continuous technological advancement, researchers can now rely on a wide range of data sets of human genome variability, each one with its benefits and drawbacks.

The first genome-wide scans for positive selection in the human genome were based on the analysis of SNP data, a collection of pre-chosen sites genotyped in a large sample from different geographical locations. Widely used data sets within this context are the HapMap Consortium data collection (International HapMap 3 Consortium et al., 2010; International HapMap Consortium et al., 2007) and the HGDP-CEPH Panel resource (Cann et al., 2002; Rosenberg, 2006). These data sets suffer from an intrinsic bias, as genotyped SNPs are based on previously characterized polymorphisms, they do not represent an unbiased sample of the overall genomic diversity (Clark et al., 2005).

Conversely, sequencing projects, such as the NHLBI-Exome Sequencing Project have the ability to recover unbiased allelic variation across the vast majority of genes (Fu et al., 2013). With the introduction of high-throughput sequencing machines (Metzker, 2010), complete whole-genome sequences of multiple individuals allow the identification of rare and population-specific genetic variants in the human genome. For instance, the 1000 Genomes Project characterized more than 50 million SNPs from whole-genome sequencing data of more than 1000 individuals (1000 Genomes Project Consortium et al., 2015, 2012, 2010), and the database is continuously growing.

While the large volume of sequence data generated by modern sequencing technologies is undoubtedly attractive, there are several challenging issues associated to such data. The data files generated are huge and the development of ad hoc computational tools is required to properly process the information (Nielsen et al., 2011). Despite these limitations, large-scale genomic data produced by high-throughput sequencing machines provide researchers with the opportunity to unveil signatures of natural selection in the genome of different human populations at an unprecedentedly fine-scale resolution.

SIGNATURES OF PATHOGEN-DRIVEN NATURAL SELECTION IN THE HUMAN GENOME

The Selective Pressure Imposed by Pathogens

By using the aforementioned methods and data sets, genome-wide scans for signatures of natural selection in the human genome identified genes under nonneutral evolution associated to particular biological pathways. For instance, loci involved in metabolism-related processes and pigmentation are often found to have been targeted by positive selection in human populations, as a consequence of adaptation to lifestyle (eg, diet) (Bersaglieri et al., 2004; Tishkoff et al., 2007) and environment (eg, UV light exposure) (Wilde et al., 2014).

Moreover, extensive signatures of adaptive evolution are also often detected in immunity-related genes (Barreiro and Quintana-Murci, 2010). This observation confirms an old hypothesis of pathogens having imposed strong selective pressure throughout human evolution. Adaptation to infectious agents has left remarkably many genomic footprints and shaped genetic variation across many loci in the human genome (Daub et al., 2013; Fumagalli et al., 2011). Furthermore, signatures of pathogen-driven selection (where infective agents represent the most likely selective pressure) have been identified in genes not strictly related to immune defense as well (Ferrer-Admetlla et al., 2009).

The idea that infectious pathogens acted as the strongest selective force on human populations is perhaps not entirely surprising. Infectious diseases have exerted a terrible toll on human populations until recently and are still responsible for considerable loss of life. Childhood diseases, acting prior to reproductive age, in particular, represented a very strong and constant selective pressure (Galvani and Slatkin, 2003). These selective pressures were not constant over space and time. The maintenance of many epidemic infectious diseases is dependent on host population density (May and Anderson, 1983) and human populations at higher densities have historically paid a higher burden.

The distribution of pathogens is also highly heterogeneous in space. The highest diversity of human infectious diseases is found close to the equator (Guernier et al., 2004). Human migrations have also led to a complex dynamics of loss and gain of specific pathogens. For example, the early colonizers of the Americas came from Asia through the Bering Strait, which is too far north to allow malaria parasites to fulfill its cycle in mosquitoes. As such, early settlers of the Americas were not affected by malaria, which only arrived later with the European colonization and the slave trade (Yalcindag et al., 2012). Conversely, many novel zoonotic diseases started infecting humans as our ancestors ventured further into various regions of the world, and interestingly, the region of the world with the largest number of endemic infectious diseases is Central America (Prugnolle et al., 2005). Pathogens are therefore responsible for exerting a continuous and at the same time variable pressure during human evolution. The effects of pathogen-driven selection on the human genome are highly variable and depend on a host of factors (Novembre and Han, 2012).

Evolution of the Adaptive Immune System

Arguably the most notable example of pathogen-driven selection in the human genome is the case of the MHC, also referred to as the HLA system. The human MHC is located on the short arm of chromosome 6, spanning a large region of around four mega base pairs and including more than 100 genes. Not only are most of the MHC genes involved in the immune system, but they also are key players in the adaptive immune response. Indeed, T cells, triggered from cell signals of altered function or infection, participate in the lysis of the infected cell or the secretion of cytokines to activate other immune cells. However, T lymphocytes can recognize pathogen peptides only when bound with a specific MHC molecule.

Genes in the HLA system, along with their interactors, are highly polymorphic: more than 2000 alleles have been described for the two most variable genes, *HLA-A* and *HLA-B* (Meyer and Thomson, 2001). High levels of polymorphisms in the human MHC can be interpreted in a functional context: individuals who are heterozygote at the MHC genes have the opportunity to respond to a broader range of infective agents, since specific MHC-peptide combinations are needed to activate an immune response (Qutob et al., 2012).

The observation that the enrichment of polymorphic sites and high-frequency alleles in the HLA genes has a functional role raises the question of whether such patterns of genetic diversity are expected under neutral evolution or are the results of a selective process. Several lines of evidence suggest that the high genetic diversity in HLA genes has been maintained by natural selection in humans (Meyer et al., 2006). For instance, an excess of nonsynonymous (and thus functional) substitutions occurring in the functional region for antigen binding compared to synonymous (and thus silent) substitutions indicates that natural selection favored the maintenance of these functional changes at the protein level (Hughes and Nei, 1989).

Perhaps the strongest argument for the action of selection in the HLA gene is the presence of multiple trans-specific polymorphisms shared between humans and chimpanzees (Azevedo et al., 2015). The age of these alleles has been estimated to predate the divergence time between human and chimpanzee. For this reason, trans-specific polymorphisms are unlikely to occur under neutrality and are a typical hallmark of long-term balancing selection (Charlesworth, 2006). Overdominance, or heterozygote advantage, is the most likely cause for the onset of balancing selection in the HLA genes (Penn et al., 2002).

Finally, since pathogens are expected to vary in number across geographical locations, identifying alleles, which correlate in frequency with the local pathogen load, is a useful strategy to test for pathogen-driven selection in the human MHC. Following this reasoning, populations from areas with high pathogen diversity are expected to harbor an increased HLA genetic diversity as such individuals would be able to cope with a broader range of pathogens. The proportion of HLA diversity, which is not explained by demographic factors, is significantly and positively correlated with pathogen richness, a measure for the abundance of different pathogenic species in a geographical location (Prugnolle et al., 2005). Human populations exposed to a more diverse spectrum of pathogens exhibit higher HLA diversity than those exposed to fewer pathogens. This suggests that the high levels of HLA genetic diversity are primarily maintained by pathogen-driven balancing selection.

Balancing selection is a major force shaping the genetic diversity of immune-related genes even outside the HLA region. As an illustration, two common haplotypes in *TAP2*, a gene encoding for a protein which forms a transporter complex involved in the translocation of antigenic

peptides, have been maintained in humans by balancing selection (Cagliani et al., 2011). The putative causal variants targeted by selection affect *TAP2* splicing, suggesting that balancing selection acted to maintain different isoforms of *TAP2*, presumably to increase the ability to respond to a larger set of pathogens (Cagliani et al., 2011).

Evolution of the Innate Immune System

The innate immune system is the other important component of the host defense and interaction between host and microbiota. The innate system constitutes the first barrier of immunity and precedes the adaptive immune response: changes at the innate immunity level influence the B and T cells activation at the adaptive system level. Toll-like receptors (TLR), RIG-I-like receptors, and NOD-like receptors are part of the innate immunity system among others. These receptors induce the activation of effector molecules, such as interferons, which eliminate pathogenic agents.

Innate immunity genes evolved under a complex dynamic, with several genes targeted by negative purifying selection and others following a scenario of relaxation of constraints (Quintana-Murci and Clark, 2013). TLRs comprise a wide variety of molecules, mainly divided in those expressed on the cell surface, and those expressed within the cell. Cell-surface TLRs exhibit high levels of nucleotide diversity presumably due to relaxation of functional constraints (or balancing selection). On the other hand, within-cell TLRs are targeted by purifying selection, where even mildly damaging mutations are rapidly removed from the population. Finally, TLRs activate signaling pathways mediated by the toll/interleukin-1 receptor (TIR)-containing adapters, which are another example of targets for positive selection in human populations (Fornarino et al., 2011). Similar to TLRs, the genetic variation at human defensins, a gene family with a wide spectrum of antimicrobial activities, has been shaped by events of purifying, positive, and balancing selection (Cagliani et al., 2008; Hollox and Armour, 2008). Overall, the complex selection patterns in the innate immunity molecules indicate the need to maintain their functionality, allowing, in some cases, for an increased genetic diversity to provide a rapid and effective response to a wide spectrum of pathogens (Ferrer-Admetlla et al., 2008).

Pathogen-Driven Selection Outside the Immune System

In the late 1940s, J. B. S. Haldane, a pioneer in many fields of science including genetics, first hypothesized that infectious diseases have exerted a major burden on humans, and that the selective pressure imposed by pathogenic agents might be responsible for the maintenance of deleterious mutations in current human populations (Haldane, 1949). He suggested that the prevalence of thalassemia, a blood disorder widespread in Mediterranean regions, resulted from the selective pressure imposed by malaria (Haldane, 1949).

The specific example pointed out by Haldane highlights a direct link between an infectious agent (the malaria-causing agent *P. falciparum*) and natural selection in human genes. The allele that causes the defective hemoglobin is maintained in the population by balancing selection at a frequency of 10% in regions with a high prevalence of *P. falciparum*, with heterozygous individuals having a reduced risk of developing severe malaria. This case further points to an important observation about pathogen-driven selection as thalassemia is caused by mutations in globin genes, which do not encode immune response effectors: pathogen-driven selection does not solely target immune-related genes. Perhaps one of the most striking examples of pathogen-driven selection genes not directly linked to immune functions is the case of blood group antigen (BGA) genes.

In humans, 29 blood group systems have been identified, each one specified by a BGA constituted by a protein or carbohydrate molecule expressed on the membrane of the erythrocyte. For most systems, the molecular bases are known with polymorphisms accounting for the individual blood group phenotype (Blumenfeld and Patnaik, 2004). BGA genes belong to different functional categories, such as receptors, transporters, channels, adhesion molecules, and enzymes. The number of different alleles, including missense or nonsense mutations, is highly variable among BGA genes. BGA polymorphisms have been extensively studied as their association with infections susceptibility has been reported for several diseases, for instance with malaria (Moulds and Moulds, 2000) and Norwalk virus (Lindesmith et al., 2003). BGA genes have been frequently targeted by pathogen-driven natural selection to maintain variability at multiple loci (Fumagalli et al., 2009a).

The ABO blood group was one of the first cases of human polymorphisms ever identified, with a large variability of A and B blood group frequencies across human populations. Human ABO genetic diversity is over an order of magnitude higher than the genomic average polymorphic rate (Calafell et al., 2008; Ségurel et al., 2012). Moreover, multiple common haplotypes are maintained in human populations, as a consequence of high genetic diversity promoting haplotypic differentiation (Fig. 11.2). In other primates (such as chimpanzees and orangutans) ABO antigens are also highly polymorphic, with the same two amino acid changes responsible for A and B blood group phenotypes. A and B blood groups result from a trans-specific polymorphism that has been selectively maintained for over 20 million years (Ségurel et al., 2012). Trans-specific polymorphisms are rare outside the MHC

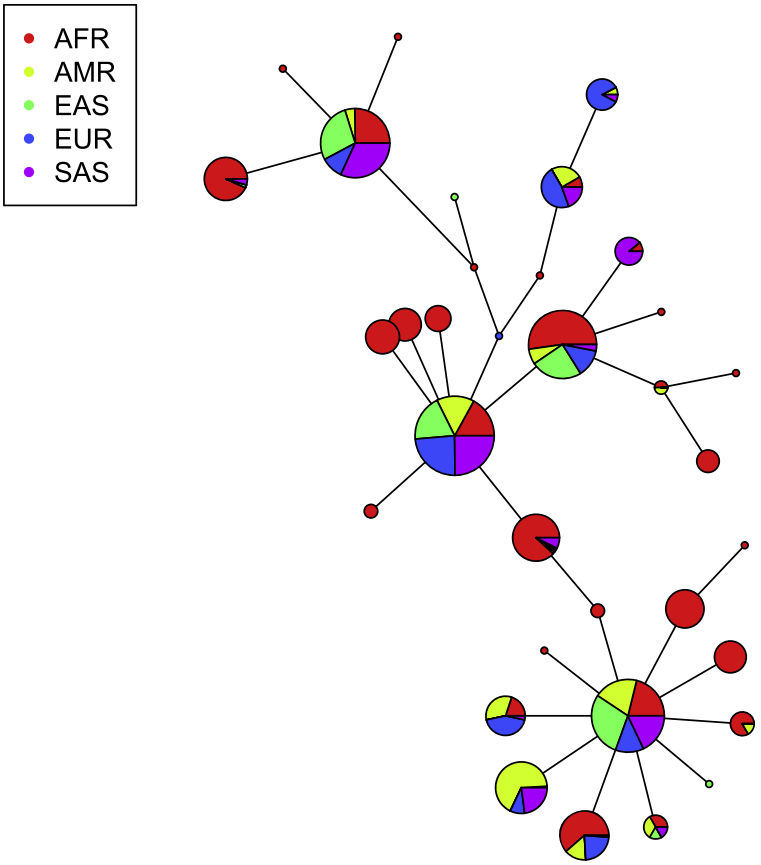

FIGURE 11.2 Network of ABO haplotypes in human populations. A median-joining network of ABO haplotypes in distinct human macro-populations is shown. Each circle represents a distinct haplotype with size proportional (in log2 scale for graphic purposes) to its frequency, and it is color-coded according to its frequency in the following populations: Africans (AFR), Americans (AMR), East Asians (EAS), Europeans (EUR), and South Asians (SAS). Haplotypes are connected by arcs whose lengths are proportional to how many mutations separate them. Haplotypes were extracted from the 1000 Genomes Project database and only coding mutations (either missense or nonsense) were retained.

system and are a hallmark of long-term balancing selection. The long-standing selective pressure on ABO is at least partially explained by adaptation to pathogens, as ABO blood groups modulate the susceptibility to several pathogens, including *P. falciparum*, *H. pylori*, and *V. cholerae* (Borén et al., 1993; Moulds et al., 1996).

The expression of ABO antigens in secretions depends on the action of a fucosyltransferase encoded by *FUT2* gene. *FUT2* antigens belong to the Lewis blood group system. A common *FUT2* null allele is responsible for most nonsecretor phenotypes in Europe and Africa, while a missense allele is common in East Asians (Koda et al., 2001). Homozygous individuals for the null variants present the nonsecretor phenotype, which means that they cannot express ABO antigens in secretions. While most *FUT2* variants have been subjected to a long history of balancing selection among Eurasian and African populations, one novel variant is spreading fast in East Asia due to positive selection (Ferrer-Admetlla et al., 2009). Nevertheless, selection on *FUT2* is at least partially pathogen-driven.

Adaptation to Local Pathogenic Environments

Different kinds of pathogens (viruses, protozoa, helminths) are expected to affect a different range of biological pathways. Viruses have exerted a continuous selective pressure on human genes throughout evolution, as some have affected humans even before they emerged as a species. A substantial fraction of repeat elements in the human genome (representing between 5% and 10% of the entire sequence) is comprised by endogenous retroviruses left by past infections (Lander et al., 2001).

Genetic adaptation to viruses is extremely challenging due to the viruses' fast evolutionary rate. Nevertheless, only a few Genome-Wide Association Studies (GWAS) identified mutations associated with increased susceptibility to viral infections, with most of the detected variants located in the HLA region (Fellay et al., 2007). On the other hand, the identification of SNPs subjected to virus-driven selective pressure led to the discovery of a complex network enriched in viral products-interacting

proteins (Fumagalli et al., 2010a). Most of the genes responsible for adaptation to viruses display very low connectivity (and thus fewer interactions) with other genes, in line with the observation that genes found on less-connected nodes in networks are more likely to evolve rapidly in response to changes in the environment (Fumagalli et al., 2010a).

In human populations, resistance to infectious diseases, and in particular to viral infections, is thought to be under a complex and multigenic control with single SNPs playing a small protective role. Despite the strong selective pressure that viruses exerted, variants with a well-established role in resistance to viral infections may be evolving neutrally. This is the case for a deletion in the *CCR5* gene, the C-to-C chemokine receptor 5, where a 32-base pair deletion confers resistance to HIV in homozygous carriers. The haplotype carrying the resistance allele, which confers strong protection against HIV-1 infection and possibly against other pathogens, displays no signature of selection (Sabeti et al., 2005). Nevertheless, there are several examples of variants modulating virus resistance being targeted by selection. Some of these examples involve variants associated with HIV progression or multiple sclerosis, like in the case of a zinc-finger gene, *ZC3HAV1*, which exhibits one human-chimpanzee trans-specific polymorphism that modulates susceptibility to multiple sclerosis in Europeans (Cagliani et al., 2012).

In addition to viruses, infection with protozoa, and especially malaria parasites, has imposed strong selective pressures. Malaria still exacts a huge toll on human health with nearly 500 million people infected worldwide and up to one million dying each year, most of them young children. In the absence of any effective vaccine, antimalarial drugs represent a major tool to reduce malaria incidence and eventually eradicate the disease. However, *P. falciparum*, the main malaria parasite, has the potential to develop resistance to antimalarial drugs by evolutionary adaptation. For all these reasons, malaria is considered to exert one of the strongest selective pressures in the recent history of humans (Kwiatkowski, 2005).

The high frequency of deleterious mutations for thalassemia in the Mediterranean region or sickle cell disorders in African populations is the result of heterozygous individuals being less susceptible to malaria (Ackerman et al., 2005). Indeed, the malaria parasite binds to molecules at the erythrocyte surface and enters the erythrocyte initiating a cascade of events to escape from the immune response. Two genes that carry an unusually high extended haplotype homozygosity with putative malaria-resistant mutations are *G6PD* and *TNFSF5* (Sabeti et al., 2002a). Such patterns of extended haplotypes with high homozygosity are suggestive of the action of positive selection. Glucose-6-phosphate dehydrogenase (or *G6PD*) is a well-known example of a gene carrying variants that confer malaria resistance. A common variant in this gene confers partial protection against malaria, with a 50% reduction in disease risk (Tishkoff et al., 2001). *TNFSF5* is the CD40 ligand gene, which has a common variant in the promoter region associated with a steady decrease of malaria infection (Sabeti et al., 2002b).

Infections by helminths (parasitic worms) represent a heavy burden on humans. Two billion individuals are infected worldwide and helminths are responsible for the highest prevalence of chronic infectious diseases (Hotez et al., 2008). Despite parasitic worms leading to severe clinical symptoms only in a minority of heavily infected individuals, even low exposure to parasite burdens can result in impaired nutritional status and growth retardation. Helminths evolve more slowly than viral agents and their complex life cycle results in a stable temporal and spatial geographical distribution (Dunne and Cooke, 2005). Among the most notable examples of loci targeted by helminth-driven selection are the interleukin and their receptors genes, and genes involved in cytokine-mediated inflammation and integrin signaling (Fumagalli et al., 2010b, 2009b).

EVOLUTIONARY CAUSES OF SUSCEPTIBILITY TO INFECTIOUS DISEASES

Viruses and protozoa shaped the genetic resistance to several infectious diseases, including malaria and multiple sclerosis (Karlsson et al., 2014). In the case of helminths, which affect the genetic variability at inflammatory-related genes (Fumagalli et al., 2010b), the link between adaptation and predisposition to disease is more complex and interesting from an evolutionary point of view. Indeed, the incidence of most allergies and chronic inflammatory diseases has increased in the industrialized world. The so-called "hygiene hypothesis" was formulated to explain this observation (Sironi and Clerici, 2010).

The hypothesis states that the changes in the environmental conditions and in the healthcare system in the industrialized world have resulted in higher sterilization of the environment. This reduced exposure of the immune system to pathogens leads to an imbalance in immune responses that favors the development of chronic inflammatory disease (Bufford and Gern, 2005). The hygiene hypothesis was first formulated by epidemiologists who observed that atopic diseases were less frequent in families with a larger number of siblings, children who attended day care centers, and individuals who grew up in the countryside. These observations led to the idea that dirtier environments may have a protective effect toward the development of autoimmune diseases and allergies.

From an immunological point of view, the T regulatory cells are responsible for the regulation of the homeostasis of

the immune system, allowing the removal of invaders, but preventing the immune-mediated attack of the host. Alterations of such cells bring an inflammatory response, favoring the onset of autoimmune conditions (Sironi and Clerici, 2010).

Several reports have suggested that a portion of susceptibility alleles for autoimmune diseases might be maintained in human populations because they confer increased resistance against infection. Among the best candidate genes, several loci targeted by selection have been associated with celiac disease, ulcerative colitis, type 1 diabetes, Crohn's disease, and multiples sclerosis (Cagliani et al., 2013; Karlsson et al., 2014). Therefore, the identification of autoimmune disease–related genes targeted by natural selection is at least consistent with the hygiene hypothesis.

While risk alleles are often shared among different autoimmune diseases, some alleles predispose to one condition but protect against another disorder (Cagliani et al., 2011). One possibility for the maintenance of these potentially deleterious alleles is that they confer some other advantage, therefore resulting in a balancing selection regime, or that a fraction of these variants has behaved neutrally during most of human history because past environmental conditions did not predispose to a disease (Cagliani et al., 2011).

The removal of several pathogens from our environment might have activated many alleles that were once balanced or neutral but are deleterious today. In this evolutionary perspective, population genetics studies represent a powerful approach to pinpoint candidate variants harboring autoimmune disease susceptibility.

FUTURE PERSPECTIVES

Over the last decades, GWAS has become the standard approach to characterize the genetic basis of phenotypes of interest (Welter et al., 2014). This methodology compares the allele frequency over a large number of loci in a vast number of cases and controls, which are matched as well as possible for confounding variables such as age, sex, or ethnic origin. GWAS have not been particularly successful for detecting variants involved in susceptibility or resistance to infectious diseases (Hill, 2012). This is partly due to the difficulty of recruiting sufficiently large and well-controlled cohorts of patients for infectious diseases, which tend to be far more transient than chronic diseases. An additional complication is that pathogens are themselves often extremely genetically diverse and different strains or lineages can differ in virulence and symptoms. It is interesting in this context that arguably the most successful GWAS for infectious diseases was on leprosy (Liu et al., 2015; Zhang et al., 2009), which is possibly the least genetically variable human pathogen, with only a few SNPs differentiating strains from different continents (Monot et al., 2009; Singh et al., 2015).

To circumvent the limitations of GWAS in the field of infectious diseases, researchers have adopted alternative strategies to link genetic with functional variation. Genome-wide scans for selection identified hundreds of regions putatively carrying variants targeted by positive selection (Akey, 2009). However, only a few studies aimed at characterizing the impact of such selected variants and, for the majority of cases, the functional role of adaptive variants, has not been elucidated.

Researchers are now tackling the issue of identifying functional variants by adopting an integrative approach. Sites predicted to be under selection could then be tested for molecular functionality using gene annotation, protein structure, epigenetics, and genetic association data. The resulting causal variant will then be prioritized and selected for an experimental follow-up. In 2013, Grossman and coworkers selected a few candidate variants from a list of almost 500 regions under selection in human populations (Grossman et al., 2013). They produced a shorter list of candidate variants by using functional annotation, giving priority to coding and regulatory mutations as well as noncoding RNAs and sites associated with a variety of phenotypes. One of the variants is located in the toll-like receptor 5 (*TLR5*), which plays a role in the innate immune system. Their scan for selection identified a nonsynonymous variant highly conserved in the primate lineage. Authors then experimentally characterized this candidate variant in *TLR5*, and showed that it leads to altered proinflammatory signaling in response to stimulation with bacterial flagellin (Grossman et al., 2013).

This example shows how research is moving from a pure computational prediction of selection targets at the genome-wide level, to deep analysis of a few candidate variants which can be functionally characterized by in vitro or in vivo experiments. This integrative approach appears to be particularly promising for polymorphisms affecting susceptibility to infectious diseases, since resistance to pathogenic infections (and in general the coevolution between humans and pathogens) is thought to involve complex and nonstable genetic patterns, which would be hard to capture with traditional association studies.

REFERENCES

Ackerman, H., Usen, S., Jallow, M., et al., 2005. A comparison of case-control and family-based association methods: the example of sickle-cell and malaria. Annals of Human Genetics 69, 559–565.

Akey, J.M., 2009. Constructing genomic maps of positive selection in humans: where do we go from here? Genome Research 19, 711–722.

Alonso, S., Izagirre, N., Smith-Zubiaga, I., et al., 2008. Complex signatures of selection for the melanogenic loci TYR, TYRP1 and DCT in humans. BMC Evolutionary Biology 8, 74.

Andrés, A.M., Hubisz, M.J., Indap, A., et al., 2009. Targets of balancing selection in the human genome. Molecular Biology and Evolution 26, 2755–2764.

Azevedo, L., Serrano, C., Amorim, A., Cooper, D.N., 2015. Trans-species polymorphism in humans and the great apes is generally maintained by balancing selection that modulates the host immune response. Human Genomics 9, 21.

Balaresque, P.L., Ballereau, S.J., Jobling, M.A., 2007. Challenges in human genetic diversity: demographic history and adaptation. Human Molecular Genetics 16 (Spec. No. 2), R134–R139.

Balding, D.J., 2003. Likelihood-based inference for genetic correlation coefficients. Theoretical Population Biology 63, 221–230.

Barreiro, L.B., Laval, G., Quach, H., Patin, E., Quintana-Murci, L., 2008. Natural selection has driven population differentiation in modern humans. Nature Genetics 40, 340–345.

Barreiro, L.B., Quintana-Murci, L., 2010. From evolutionary genetics to human immunology: how selection shapes host defence genes. Nature Reviews Genetics 11, 17–30.

Benedictow, O.J., 2004. The Black Death, 1346–1353: The Complete History. Boydell Press.

Bersaglieri, T., Sabeti, P.C., Patterson, N., et al., 2004. Genetic signatures of strong recent positive selection at the lactase gene. American Journal of Human Genetics 74, 1111–1120.

Blumenfeld, O.O., Patnaik, S.K., 2004. Allelic genes of blood group antigens: a source of human mutations and cSNPs documented in the Blood Group Antigen Gene Mutation Database. Human Mutation 23, 8–16.

Borén, T., Falk, P., Roth, K.A., Larson, G., Normark, S., 1993. Attachment of *Helicobacter pylori* to human gastric epithelium mediated by blood group antigens. Science 262, 1892–1895.

Bufford, J.D., Gern, J.E., 2005. The hygiene hypothesis revisited. Immunology and Allergy Clinics of North America 25, 247–262 v–vi.

Cagliani, R., Fumagalli, M., Biasin, M., et al., 2010. Long-term balancing selection maintains trans-specific polymorphisms in the human TRIM5 gene. Human Genetics 128, 577–588.

Cagliani, R., Fumagalli, M., Riva, S., et al., 2008. The signature of long-standing balancing selection at the human defensin beta-1 promoter. Genome Biology 9, R143.

Cagliani, R., Guerini, F.R., Fumagalli, M., et al., 2012. A trans-specific polymorphism in ZC3HAV1 is maintained by long-standing balancing selection and may confer susceptibility to multiple sclerosis. Molecular Biology and Evolution 29, 1599–1613.

Cagliani, R., Pozzoli, U., Forni, D., et al., 2013. Crohn's disease loci are common targets of protozoa-driven selection. Molecular Biology and Evolution 30, 1077–1087.

Cagliani, R., Riva, S., Pozzoli, U., et al., 2011. Balancing selection is common in the extended MHC region but most alleles with opposite risk profile for autoimmune diseases are neutrally evolving. BMC Evolutionary Biology 11, 171.

Calafell, F., Roubinet, F., Ramírez-Soriano, A., et al., 2008. Evolutionary dynamics of the human ABO gene. Human Genetics 124, 123–135.

Cann, H.M., de Toma, C., Cazes, L., et al., 2002. A human genome diversity cell line panel. Science 296, 261–262.

Cavalli-Sforza, L.L., Menozzi, P., Piazza, A., 1994. The History and Geography of Human Genes. Princeton University Press.

Charlesworth, D., 2006. Balancing selection and its effects on sequences in nearby genome regions. PLOS Genetics 2, e64.

Clark, A.G., Hubisz, M.J., Bustamante, C.D., Williamson, S.H., Nielsen, R., 2005. Ascertainment bias in studies of human genome-wide polymorphism. Genome Research 15, 1496–1502.

Coop, G., Witonsky, D., Di Rienzo, A., Pritchard, J.K., 2010. Using environmental correlations to identify loci underlying local adaptation. Genetics 185, 1411–1423.

Daub, J.T., Hofer, T., Cutivet, E., et al., 2013. Evidence for polygenic adaptation to pathogens in the human genome. Molecular Biology and Evolution 30, 1544–1558.

DeGiorgio, M., Lohmueller, K.E., Nielsen, R., 2014. A model-based approach for identifying signatures of ancient balancing selection in genetic data. PLOS Genetics 10, e1004561.

Dunne, D.W., Cooke, A., 2005. A worm's eye view of the immune system: consequences for evolution of human autoimmune disease. Nature Reviews Immunology 5, 420–426.

Faria, N.R., Rambaut, A., Suchard, M.A., et al., 2014. The early spread and epidemic ignition of HIV-1 in human populations. Science 346, 56–61.

Fay, J.C., Wu, C.I., 2000. Hitchhiking under positive Darwinian selection. Genetics 155, 1405–1413.

Fellay, J., Shianna, K.V., Ge, D., et al., 2007. A whole-genome association study of major determinants for host control of HIV-1. Science 317, 944–947.

Ferrer-Admetlla, A., Bosch, E., Sikora, M., et al., 2008. Balancing selection is the main force shaping the evolution of innate immunity genes. Journal of Immunology (Baltimore, MD) 1950 (181), 1315–1322.

Ferrer-Admetlla, A., Sikora, M., Laayouni, H., et al., 2009. A natural history of FUT2 polymorphism in humans. Molecular Biology and Evolution 26, 1993–2003.

Fornarino, S., Laval, G., Barreiro, L.B., et al., 2011. Evolution of the TIR domain-containing adaptors in humans: swinging between constraint and adaptation. Molecular Biology and Evolution 28, 3087–3097.

Frichot, E., Schoville, S.D., Bouchard, G., François, O., 2013. Testing for associations between loci and environmental gradients using latent factor mixed models. Molecular Biology and Evolution 30, 1687–1699.

Fumagalli, M., Cagliani, R., Pozzoli, U., et al., 2009a. Widespread balancing selection and pathogen-driven selection at blood group antigen genes. Genome Research 19, 199–212.

Fumagalli, M., Pozzoli, U., Cagliani, R., et al., 2010a. Genome-wide identification of susceptibility alleles for viral infections through a population genetics approach. PLOS Genetics 6, e1000849.

Fumagalli, M., Pozzoli, U., Cagliani, R., et al., 2010b. The landscape of human genes involved in the immune response to parasitic worms. BMC Evolutionary Biology 10, 264.

Fumagalli, M., Pozzoli, U., Cagliani, R., et al., 2009b. Parasites represent a major selective force for interleukin genes and shape the genetic predisposition to autoimmune conditions. Journal of Experimental Medicine 206, 1395–1408.

Fumagalli, M., Sironi, M., 2014. Human genome variability, natural selection and infectious diseases. Current Opinion In Immunology 30, 9–16.

Fumagalli, M., Sironi, M., Pozzoli, U., et al., 2011. Signatures of environmental genetic adaptation pinpoint pathogens as the main selective pressure through human evolution. PLOS Genetics 7, e1002355.

Fu, W., O'Connor, T.D., Jun, G., et al., 2013. Analysis of 6,515 exomes reveals the recent origin of most human protein-coding variants. Nature 493, 216–220.

Fu, Y.X., Li, W.H., 1993. Statistical tests of neutrality of mutations. Genetics 133, 693–709.

Genomes Project Consortium, Abecasis, G.R., Altshuler, D., et al., 2010. A map of human genome variation from population-scale sequencing. Nature 467, 1061–1073.

Genomes Project Consortium, Abecasis, G.R., Auton, A., et al., 2012. An integrated map of genetic variation from 1,092 human genomes. Nature 491, 56–65.

Genomes Project Consortium, Auton, A., Brooks, L.D., et al., 2015. A global reference for human genetic variation. Nature 526, 68–74.

Galvani, A.P., Slatkin, M., 2003. Evaluating plague and smallpox as historical selective pressures for the CCR5-Δ32 HIV-resistance allele. Proceedings of the National Academy of Sciences of the United States of America 100, 15276–15279.

Gao, Z., Przeworski, M., Sella, G., 2015. Footprints of ancient-balanced polymorphisms in genetic variation data from closely related species. Evolution: International Journal of Organic Evolution 69, 431–446.

Garud, N.R., Messer, P.W., Buzbas, E.O., Petrov, D.A., 2015. Recent selective sweeps in north American *Drosophila melanogaster* show signatures of soft sweeps. PLOS Genetics 11, e1005004.

Garud, N.R., Rosenberg, N.A., 2015. Enhancing the mathematical properties of new haplotype homozygosity statistics for the detection of selective sweeps. Theoretical Population Biology 102, 94–101.

Gerbault, P., 2013. The onset of lactase persistence in Europe. Human Heredity 76, 154–161.

Grossman, S.R., Andersen, K.G., Shlyakhter, I., et al., 2013. Identifying recent adaptations in large-scale genomic data. Cell 152, 703–713.

Grossman, S.R., Shlyakhter, I., Karlsson, E.K., et al., 2010. A composite of multiple signals distinguishes causal variants in regions of positive selection. Science 327, 883–886.

Guernier, V., Hochberg, M.E., Guégan, J.-F., 2004. Ecology drives the worldwide distribution of human diseases. PLoS Biology 2, e141.

Gutenkunst, R.N., Hernandez, R.D., Williamson, S.H., Bustamante, C.D., 2009. Inferring the joint demographic history of multiple populations from multidimensional SNP frequency data. PLOS Genetics 5, e1000695.

Haldane, J.B.S., 1949. The rate of mutation of human genes. Hereditas 35, 267–273.

Hancock, A.M., Alkorta-Aranburu, G., Witonsky, D.B., Di Rienzo, A., 2010. Adaptations to new environments in humans: the role of subtle allele frequency shifts. Philosophical Transactions of the Royal Society of London B Biological Sciences 365, 2459–2468.

Hancock, A.M., Witonsky, D.B., Alkorta-Aranburu, G., et al., 2011. Adaptations to climate-mediated selective pressures in humans. PLOS Genetics 7, e1001375.

Hancock, A.M., Witonsky, D.B., Gordon, A.S., et al., 2008. Adaptations to climate in candidate genes for common metabolic disorders. PLOS Genetics 4, e32.

Hardy, K., Brand-Miller, J., Brown, K.D., Thomas, M.G., Copeland, L., 2015. The importance of dietary carbohydrate in human evolution. Quarterly Review of Biology 90, 251–268.

Harris, E.E., Meyer, D., 2006. The molecular signature of selection underlying human adaptations. American Journal of Physical Anthropology 43, 89–130.

Harris, K., Nielsen, R., 2013. Inferring demographic history from a spectrum of shared haplotype lengths. PLOS Genetics 9, e1003521.

Hernandez, R.D., Kelley, J.L., Elyashiv, E., et al., 2011. Classic selective sweeps were rare in recent human evolution. Science 331, 920–924.

Hill, A.V.S., 2012. Evolution, revolution and heresy in the genetics of infectious disease susceptibility. Philosophical Transactions of the Royal Society of London B Biological Sciences 367, 840–849.

Hollox, E.J., Armour, J.A.L., 2008. Directional and balancing selection in human beta-defensins. BMC Evolutionary Biology 8, 113.

Hotez, P.J., Brindley, P.J., Bethony, J.M., et al., 2008. Helminth infections: the great neglected tropical diseases. The Journal of Clinical Investigation 118, 1311–1321.

Hudson, R.R., Kreitman, M., Aguadé, M., 1987. A test of neutral molecular evolution based on nucleotide data. Genetics 116, 153–159.

Huerta-Sánchez, E., Jin, X., Asan, et al., 2014. Altitude adaptation in Tibetans caused by introgression of Denisovan-like DNA. Nature 512, 194–197.

Hughes, A.L., Nei, M., 1989. Nucleotide substitution at major histocompatibility complex class II loci: evidence for overdominant selection. Proceedings of the National Academy of Sciences of the United States of America 86, 958–962.

International HapMap 3 Consortium, Altshuler, D.M., Gibbs, R.A., et al., 2010. Integrating common and rare genetic variation in diverse human populations. Nature 467, 52–58.

International HapMap Consortium, Frazer, K.A., Ballinger, D.G., et al., 2007. A second generation human haplotype map of over 3.1 million SNPs. Nature 449, 851–861.

Izagirre, N., García, I., Junquera, C., de la Rúa, C., Alonso, S., 2006. A scan for signatures of positive selection in candidate loci for skin pigmentation in humans. Molecular Biology and Evolution 23, 1697–1706.

Karlsson, E.K., Kwiatkowski, D.P., Sabeti, P.C., 2014. Natural selection and infectious disease in human populations. Nature Reviews Genetics 15, 379–393.

Kelley, J.L., Madeoy, J., Calhoun, J.C., Swanson, W., Akey, J.M., 2006. Genomic signatures of positive selection in humans and the limits of outlier approaches. Genome Research 16, 980–989.

Kim, Y., Nielsen, R., 2004. Linkage disequilibrium as a signature of selective sweeps. Genetics 167, 1513–1524.

Koda, Y., Tachida, H., Pang, H., et al., 2001. Contrasting patterns of polymorphisms at the ABO-secretor gene (FUT2) and plasma alpha(1,3)fucosyltransferase gene (FUT6) in human populations. Genetics 158, 747–756.

Kosiol, C., Vinar, T., da Fonseca, R.R., et al., 2008. Patterns of positive selection in six Mammalian genomes. PLOS Genetics 4, e1000144.

Kwiatkowski, D.P., 2005. How malaria has affected the human genome and what human genetics can teach us about malaria. American Journal of Human Genetics 77, 171–192.

Lander, E.S., Linton, L.M., Birren, B., et al., 2001. Initial sequencing and analysis of the human genome. Nature 409, 860–921.

Lindblad-Toh, K., Garber, M., Zuk, O., et al., 2011. A high-resolution map of human evolutionary constraint using 29 mammals. Nature 478, 476–482.

Lindesmith, L., Moe, C., Marionneau, S., et al., 2003. Human susceptibility and resistance to Norwalk virus infection. Nature Medicine 9, 548–553.

Liu, H., Irwanto, A., Fu, X., et al., 2015. Discovery of six new susceptibility loci and analysis of pleiotropic effects in leprosy. Nature Genetics 47, 267–271.

May, R.M., Anderson, R.M., 1983. Parasite host coevolution. In: Coevolution. Sinauer.

McDonald, J.H., Kreitman, M., 1991. Adaptive protein evolution at the Adh locus in *Drosophila*. Nature 351, 652–654.

Messer, P.W., Petrov, D.A., 2013. Frequent adaptation and the McDonald-Kreitman test. Proceedings of the National Academy of Sciences of the United States of America 110, 8615–8620.

Metzker, M.L., 2010. Sequencing technologies - the next generation. Nature Reviews Genetics 11, 31–46.

Meyer, D., Single, R.M., Mack, S.J., Erlich, H.A., Thomson, G., 2006. Signatures of demographic history and natural selection in the human major histocompatibility complex Loci. Genetics 173, 2121–2142.

Meyer, D., Thomson, G., 2001. How selection shapes variation of the human major histocompatibility complex: a review. Annals of Human Genetics 65, 1–26.

Monot, M., Honoré, N., Garnier, T., et al., 2009. Comparative genomic and phylogeographic analysis of *Mycobacterium leprae*. Nature Genetics 41, 1282–1289.

Moulds, J.M., Moulds, J.J., 2000. Blood group associations with parasites, bacteria, and viruses. Transfusion Medicine Reviews 14, 302–311.

Moulds, J.M., Nowicki, S., Moulds, J.J., Nowicki, B.J., 1996. Human blood groups: incidental receptors for viruses and bacteria. Transfusion (Paris) 36, 362–374.

Nielsen, R., 2005. Molecular signatures of natural selection. Annual Review of Genetics 39, 197–218.

Nielsen, R., Paul, J.S., Albrechtsen, A., Song, Y.S., 2011. Genotype and SNP calling from next-generation sequencing data. Nature Reviews Genetics 12, 443–451.

Nielsen, R., Williamson, S., Kim, Y., et al., 2005. Genomic scans for selective sweeps using SNP data. Genome Research 15, 1566–1575.

Novembre, J., Di Rienzo, A., 2009. Spatial patterns of variation due to natural selection in humans. Nature Reviews Genetics 10, 745–755.

Novembre, J., Han, E., 2012. Human population structure and the adaptive response to pathogen-induced selection pressures. Philosophical Transactions of the Royal Society of London B Biological Sciences 367, 878–886.

Pagani, L., Schiffels, S., Gurdasani, D., et al., 2015. Tracing the route of modern humans out of Africa by using 225 human genome sequences from Ethiopians and Egyptians. American Journal of Human Genetics 96, 986–991.

Pavlidis, P., Živkovic, D., Stamatakis, A., Alachiotis, N., 2013. SweeD: likelihood-based detection of selective sweeps in thousands of genomes. Molecular Biology and Evolution 30, 2224–2234.

Payseur, B.A., Nachman, M.W., 2002. Natural selection at linked sites in humans. Gene 300, 31–42.

Penn, D.J., Damjanovich, K., Potts, W.K., 2002. MHC heterozygosity confers a selective advantage against multiple-strain infections. Proceedings of the National Academy of Sciences of the United States of America 99, 11260–11264.

Peter, B.M., Huerta-Sanchez, E., Nielsen, R., 2012. Distinguishing between selective sweeps from standing variation and from a de novo mutation. PLOS Genetics 8, e1003011.

Pollard, K.S., Hubisz, M.J., Rosenbloom, K.R., Siepel, A., 2010. Detection of nonneutral substitution rates on mammalian phylogenies. Genome Research 20, 110–121.

Pritchard, J.K., Pickrell, J.K., Coop, G., 2010. The genetics of human adaptation: hard sweeps, soft sweeps, and polygenic adaptation. Current Biology 20, R208–R215.

Prugnolle, F., Manica, A., Charpentier, M., et al., 2005. Pathogen-driven selection and worldwide HLA class I diversity. Current Biology 15, 1022–1027.

Quintana-Murci, L., Clark, A.G., 2013. Population genetic tools for dissecting innate immunity in humans. Nature Reviews Immunology 13, 280–293.

Qutob, N., Balloux, F., Raj, T., et al., 2012. Signatures of historical demography and pathogen richness on MHC class I genes. Immunogenetics 64, 165–175.

Raghavan, M., Steinrücken, M., Harris, K., et al., 2015. Genomic evidence for the Pleistocene and recent population history of Native Americans. Science 349, aab3884.

Raj, S.M., Pagani, L., Gallego Romero, I., Kivisild, T., Amos, W., 2013. A general linear model-based approach for inferring selection to climate. BMC Genetics 14, 87.

Reynolds, J., Weir, B.S., Cockerham, C.C., 1983. Estimation of the coancestry coefficient: basis for a short-term genetic distance. Genetics 105, 767–779.

Rosenberg, N.A., 2006. Standardized subsets of the HGDP-CEPH Human Genome Diversity Cell Line Panel, accounting for atypical and duplicated samples and pairs of close relatives. Annals of Human Genetics 70, 841–847.

Sabeti, P.C., Reich, D.E., Higgins, J.M., et al., 2002a. Detecting recent positive selection in the human genome from haplotype structure. Nature 419, 832–837.

Sabeti, P.C., Varilly, P., Fry, B., et al., 2007. Genome-wide detection and characterization of positive selection in human populations. Nature 449, 913–918.

Sabeti, P.C., Walsh, E., Schaffner, S.F., et al., 2005. The case for selection at CCR5-Delta32. PLoS Biology 3, e378.

Sabeti, P., Usen, S., Farhadian, S., et al., 2002b. CD40L association with protection from severe malaria. Genes Immunology 3, 286–291.

Ségurel, L., Thompson, E.E., Flutre, T., et al., 2012. The ABO blood group is a trans-species polymorphism in primates. Proceedings of the National Academy of Sciences of the United States of America 109, 18493–18498.

Singh, P., Benjak, A., Schuenemann, V.J., et al., 2015. Insight into the evolution and origin of leprosy bacilli from the genome sequence of *Mycobacterium lepromatosis*. Proceedings of the National Academy of Sciences of the United States of America 112, 4459–4464.

Sironi, M., Clerici, M., 2010. The hygiene hypothesis: an evolutionary perspective. Microbes and Infection/Institut Pasteur 12, 421–427.

Tajima, F., 1989. Statistical method for testing the neutral mutation hypothesis by DNA polymorphism. Genetics 123, 585–595.

Tang, K., Thornton, K.R., Stoneking, M., 2007. A new approach for using genome scans to detect recent positive selection in the human genome. PLoS Biology 5, e171.

Tishkoff, S.A., Reed, F.A., Ranciaro, A., et al., 2007. Convergent adaptation of human lactase persistence in Africa and Europe. Nature Genetics 39, 31–40.

Tishkoff, S.A., Varkonyi, R., Cahinhinan, N., et al., 2001. Haplotype diversity and linkage disequilibrium at human G6PD: recent origin of alleles that confer malarial resistance. Science 293, 455–462.

Voight, B.F., Kudaravalli, S., Wen, X., Pritchard, J.K., 2006. A map of recent positive selection in the human genome. PLoS Biology 4, e72.

Waldman, C., 2009. Atlas of the North American Indian. Checkmark Books, New York.

Weir, B.S., Hill, W.G., 2002. Estimating F-statistics. Annual Review of Genetics 36, 721–750.

Welter, D., MacArthur, J., Morales, J., et al., 2014. The NHGRI GWAS Catalog, a curated resource of SNP-trait associations. Nucleic Acids Research 42, D1001–D1006.

White, T.D., Asfaw, B., DeGusta, D., et al., 2003. Pleistocene *Homo sapiens* from Middle Awash, Ethiopia. Nature 423, 742–747.

Wilde, S., Timpson, A., Kirsanow, K., et al., 2014. Direct evidence for positive selection of skin, hair, and eye pigmentation in Europeans during the last 5,000 y. Proceedings of the National Academy of Sciences of the United States of America 111, 4832–4837.

Williams, G.C., 1975. Sex and Evolution. Princeton University Press, Princeton, NJ.

Williamson, S.H., Hubisz, M.J., Clark, A.G., et al., 2007. Localizing recent adaptive evolution in the human genome. PLOS Genetics 3, e90.

Wilson, B.A., Petrov, D.A., Messer, P.W., 2014. Soft selective sweeps in complex demographic scenarios. Genetics 198, 669–684.

Wright, S., 1951. The genetical structure of populations. Annals of Eugenics 15, 323–354.

Wright, S.I., Charlesworth, B., 2004. The HKA test revisited: a maximum-likelihood-ratio test of the standard neutral model. Genetics 168, 1071–1076.

Yalcindag, E., Elguero, E., Arnathau, C., et al., 2012. Multiple independent introductions of *Plasmodium falciparum* in South America. Proceedings of the National Academy of Sciences of the United States of America 109, 511–516.

Yang, Z., Bielawski, J.P., 2000. Statistical methods for detecting molecular adaptation. Trends in Ecology & Evolution 15, 496–503.

Yi, X., Liang, Y., Huerta-Sanchez, E., Jin, X., et al., 2010. Sequencing of 50 human exomes reveals adaptation to high altitude. Science 329, 75–78.

Yuan, X., Miller, D.J., Zhang, J., Herrington, D., Wang, Y., 2012. An overview of population genetic data simulation. Journal of Computational Biology 19, 42–54.

Zhang, C., Bailey, D.K., Awad, T., et al., 2006. A whole genome long-range haplotype (WGLRH) test for detecting imprints of positive selection in human populations. Bioinformatics (Oxford, England) 22, 2122–2128.

Zhang, F.-R., Huang, W., Chen, S.-M., et al., 2009. Genomewide association study of leprosy. New England Journal of Medicine 361, 2609–2618.

Chapter 12

Aging, Somatic Evolution, and Cancer

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MULTICELLULARITY AND SOMATIC EVOLUTION

While we can only speculate on the selective pressures that drove the evolution of multicellular organisms (improved predation, protection from predators, facilitated reproduction, etc.), it is clear that the evolution of multicellularity drove cooperation of cells for a common purpose (fitness), and the differentiation of cells into different cell types with specific functions in the body. Complex multicellular organisms, such as humans, consist of multiple functionally specialized cell types that are organized in *tissues*, such as epithelial layers or muscle. Tissues, in turn, are organized into more complex structures called *organs* which typically consist of several different tissues types and serve for specific body functions, such as food uptake, respiration, or reproduction. Most cells in the human body are called *somatic cells* and only serve within a human lifespan, as opposed to *germ cells* that give rise to *gametes* and are passed on to develop the next generation of progeny.

For tissues such as the skin, gut, and blood system, each specialized, or terminally differentiated, somatic cell typically cannot self-renew and serves its particular function for a certain short period of time after which it dies and is replaced by new cells. On the other hand, neuronal and muscle cells (such as in the brain and heart, respectively) are very long-lived (sometimes for the life of the organism); still, these cells cannot self-renew. The ultimate source of new cells in the body comes from cells that are capable of multiple divisions and self-renewal, called *stem cells*. In humans, like in other mammals, most types of stem cells are known to divide, giving rise to two daughter cells, each of which either remains a stem cell itself or commits to differentiation with a certain probability. In this way, stem cells serve two basic functions: they renew their own pool of stem cells for a particular type of tissue, and they maintain the tissue by supplying it with new differentiated cells.

The evolution of cooperation among multiple highly specialized cells and their stem cell compartments is realized through germ cells, on which selection acts to favor gamete combinations that harbor the most adaptive developmental programs for the multicellular organisms. Thus the evolution of a multicellular body, the cells it comprises, and its adaptation to the environment are driven by selection at the germline level. However, multicellularity has given rise to another type of evolution, one that occurs in the body within the organism's lifespan. Stem cells renewing the body tissues are typically organized in various kinds of stem cell pools which differ in the number of cells and organization in a tissue-specific manner. Each tissue, thus, is replenished with new cells derived from different stem cells and consists of cells of diverse clonal origin. As stem cell fate decisions, to differentiate or remain a stem cell, are typically stochastic and depend on external factors (Abkowitz et al., 1996; Klein and Simons, 2011; Lopez-Garcia et al., 2010; Vermeulen et al., 2013), the representation of particular stem cell clonal progeny in the pool changes over time. If after division a stem cell preferentially produces stem cells, its progeny (clone) will expand in the stem cell compartment. On the other hand, if the cell's daughter cells preferentially commit to differentiate, its clone will eventually disappear from the pool. Following such dynamics in stem cell compartments, the clonal composition of terminally differentiated cells composing tissues similarly changes over time. Mutations and alterations in the tissue microenvironment cause changes in particular cells' proclivity to expand into a stem cell clone or differentiate and can also affect the stem cells' death rates or cause senescence (Alsberg et al., 2006; DeGregori, 2012; Fleenor et al., 2014; Vermeulen et al., 2013). Altogether these changes in the clonal diversity of tissues and

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00012-0

their underlying stem cell compartments are called *somatic evolution*.

Stem cells are known to reside in highly specialized microenvironments in the human body, called the *stem cell niche*. These environments usually harbor specialized cells that serve to control the behavior of stem cells via specific signals (Li and Xie, 2005). A large part in response to this signaling, stem cells make cell fate decisions, which include cell division, differentiation, death, or senescence. These cell fate decisions are key determinants of the clonal diversity and dynamics in stem cell pools, and thus determine the character of somatic evolution. Therefore, the evolution of stem cells is shaped by two levels of selection. At the germline level, selection acts to produce stem cells that are best adapted to their niche microenvironment and in parallel fine tunes this microenvironment to the needs of stem cells for optimal tissue maintenance and the resulting body fitness. On the other hand, during an individual's lifespan, selection at the somatic level acts to favor stem cells that are capable of expanding their clonal progeny in the stem cell compartment, favoring clones that tend to produce more stem cells at the expense of tissue renewal. Typically, this process is restrained by certain physiological limits and does not significantly affect tissue maintenance and health. However, understanding the nature of somatic evolution is important because one particular type of it, *carcinogenesis*, leads to one of the most prevalent and deadly diseases: *cancer*. Carcinogenesis, like somatic evolution in general, can to some extent be compared to evolution in bacterial populations, whereby mutations provide various degrees of adaptive advantages or disadvantages to clonally reproducing cells and thus cause changes in the relative representation of particular cellular phenotypes in the population. In this context, carcinogenesis is believed to be driven by a series of uncontrolled clonal expansions of cells that acquire oncogenic mutations (Armitage, 1985; Armitage and Doll, 1954; Nowell, 1976).

Carcinogenesis typically initiates in stem cells or in *progenitors* (cells committed to differentiate but not yet terminally differentiated), and is generally known to require several oncogenic mutations and/or epigenetic changes, such as altered DNA methylation patterns. In competitive stem and progenitor pools, oncogenic mutations must give the recipient cells the ability to preferentially produce stem-like cell progeny so that their clones can expand and increase the chances that another oncogenic mutation happens in cells already harboring the first one (Nowell, 1976; Rozhok et al., 2014). Thus, since the early ideas by Nordling, Armitage, and Doll published in the mid-1950s (Armitage and Doll, 1954; Nordling, 1953), it has generally been accepted that oncogenic mutations provide this type of advantage to the recipient cells upon incidence, and carcinogenesis is thus rate-limited by the occurrence of such mutations. Oncogenic mutations have thus been the major focus of cancer biologists through this time, and somatic evolution has often been used as a synonym to carcinogenesis.

While understanding cancer and somatic evolution from this perspective was a dramatic improvement in our understanding of cancer more than half a century ago, an appreciable body of new evidence which has accumulated since then suggests that a substantial revision of this theory is in order. It is evident from the bulk of recent studies that somatic mutations, including oncogenic ones, do not have universal power to promote somatic evolution and carcinogenesis (Bissell and Hines, 2011; DeGregori, 2011; Ford et al., 2015; Gatenby and Vincent, 2003; Henry et al., 2010; Vermeulen et al., 2013). Their ability to drive clonal expansions turns out to be dependent on external factors, such as the state of tissue microenvironment (Rozhok and DeGregori, 2015; Rubin, 2001). It is also now clear that about half of all mutations and epigenetic changes in the human body accumulate early during body growth and maturation and their accumulation slows down with age (Horvath, 2013; Vijg et al., 2005), while cancers are universally postponed to postreproductive ages. This evidence was not available several decades ago and is different from the assumption used by early cancer theorists.

In the following sections, we will present recent evidence that provides clues to the links between somatic and organismal evolution, and demonstrate that somatic evolution and carcinogenesis follow the same principles known for organismal evolution. We will show that oncogenic mutations are just the basic necessary condition for carcinogenesis, just like mutations in organismal evolution, but that factors such as aging, smoking, or other carcinogenic contexts determine the rates of cancer progression and promote somatic evolution by imposing major changes to tissue microenvironments. We will present an evolutionary theory for how age and health of the human body can directly regulate various forms of selection in human tissues and thus impact somatic evolution, as well as explain why cancer incidence universally scales to the vastly different lifespans of different mammal species, and why larger longer lived animals that have more cells and produce more mutations are not more prone to cancer.

ORGANISMAL FITNESS VERSUS STEM CELL FITNESS

Fitness is a central concept in organismal evolution as it constitutes the basic property of an organism through which selection can act. In populations, *fitness* is generally understood as the likelihood that a given genotype will be passed on to subsequent generations and is primarily determined by reproduction and survival rates. An alternative definition of fitness is the ratio of the frequency of a

given genotype in a population before selection to its frequency after selection. All in all, fitness is a measure of how well an organism with a given genotype/phenotype is adapted to the complex environment it inhabits. For humans, like other animals, selection thus acts through the germline, favoring higher body fitness, the latter increasing the chances of reproduction, longevity, and capability to withstand disease. As these properties of the body ensure higher rates of transmission of the genotype to subsequent generations, this type of selection therefore is mostly active during the reproductive period of the human lifespan, and it weakens with age, as chances to reproduce drop and make body fitness no longer "visible" to germline selection (Fig. 12.1).

There are a number of mechanisms for how germline selection can promote high body fitness during reproductive ages by improving tissue maintenance. DNA damage of various forms (including failure to maintain the epigenetic code) is a primary cell-intrinsic mechanism of aging (Lopez-Otin et al., 2013; Rossi et al., 2005). One of the key cell compartments affected by genetic and epigenetic damage is stem cells, as these often persist through the entire lifespan and are the ultimate source of somatic cells for many tissues with fast cell turnover. Stem cells, though, are less important for some adult human tissues, such as muscle cells or neurons, the bulk of which are maintained in their terminally differentiated state throughout the entire lifespan. Most DNA damage happens during cell division, and there exist three primary strategies to deal with DNA damage in complex multicellular organisms such as mammals. First of all, evolution has favored a certain degree of fidelity in the DNA replication machinery to avoid errors in DNA during cell division. However, there may be limits to evolving extremely precise DNA replication and DNA repair machinery, as mutations are necessary for evolution, and total elimination of mutations in germline cells is not favored by selection in the long run. It has also been speculated that there are energetic costs for developing extremely precise DNA replication and repair machineries, which create limits to what precision can be favored by selection. However, another serious (and perhaps more important) barrier is imposed by the population size (Lynch, 2010). Large long-lived multicellular organisms tend to have small population sizes due to environmental capacity limitations relative to simpler, smaller organisms. Insect populations are typically much more numerous than those of mammals, and are vastly outnumbered in turn by single-cell organisms, such as bacteria. The power of selection is known to be positively related to population size, while the power of random processes that interfere with selection in a stochastic manner, called *drift*, is inversely proportional in strength to the effective population size. This rule means that in smaller populations mutation-induced phenotypic changes in organisms must be larger to ensure that selection for them can overcome drift. It has thus been argued that in populations of large long-lived animals, selection is more limited in its ability to increase the precision of DNA replication and repair machinery (Lynch, 2010). Evidence demonstrates that indeed large, long-lived animals, such as humans, have not evolved more efficient DNA replication and repair machineries compared to smaller short-lived organisms. And the somatic mutation rates in mammals are even higher than those in the germline (Lynch, 2010; Welch et al., 2012). So even if lowering the rate of somatic mutation would appear to be a strategy to increase the lifespan of large animals, evolution of long life spans and large multicellular bodies does not appear to have actually employed this strategy.

Alongside DNA replication and repair machineries, another strategy to control the accumulation of DNA damage and resulting tissue impairment is realized in cellular systems that are active in surveying for overly damaged cells. The most well-known of such systems is controlled by the protein p53, and if excessive DNA damage in a stem cell is detected, a p53-dependent pathway signals the affected cell to be permanently removed from

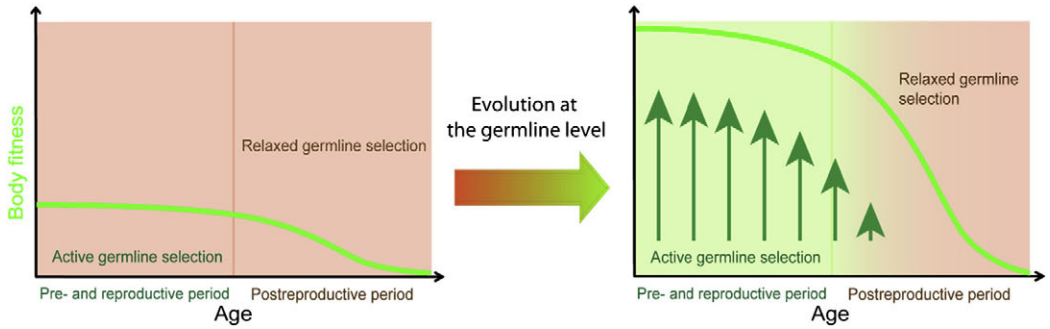

FIGURE 12.1 The effect of evolution at the germline level on body fitness at different ages. Tissue and body performance are subject to germline level selection during the pre- and reproductive portions of life, driving coevolution of stem cells and tissue microenvironment. During the post-reproductive years, changes in microenvironment and stem cell performance are not visible to germline selection.

the replicative cell pool by processes such as senescence or apoptosis (Roos and Kaina, 2013; Spike and Wahl, 2011). In this way, the total pool of stem cells is regularly "cleansed" of cells with excessive DNA damage. The p53 and other surveillance pathways can also eliminate cells with deregulated signaling pathways, providing yet another means to eliminate potentially dangerous cells. That p53 is mutationally or otherwise inactivated in the majority of cancers highlights the importance of this mechanism for eliminating cells with potentially oncogenic DNA damage (Rivlin et al., 2011).

Another important cellular mechanism that prevents tissue degradation is called *autophagy*, or *autophagocytosis* (Glick et al., 2010; Mizushima, 2007). Autophagy is a process whereby cells degrade damaged and dysfunctional cellular components in order to recycle the chemical compounds from which these components (such as organelles) are built. The process prevents cellular damage and the accumulation of dysfunctional products and organelles in cells. Interestingly, mutations in various organisms, including flies and worms, which promote autophagy also extend lifespan, while mutations that impair autophagy correspondingly lead to shorter lifespans. Moreover, dietary restriction and exercise promote both autophagy and increased lifespan from worms to mice (He et al., 2012; Morselli et al., 2010; Nair and Klionsky, 2011). Thus, autophagy may constitute a major antiaging process, and autophagy is also considered to be a tumor suppressive mechanism.

Together with strategies to cope with DNA and cellular damage, selection at the germline level for optimal tissue maintenance and body fitness acts to fine-tune the behavior of stem cells within the contexts of their niche microenvironment. This fine-tuned interaction requires a bidirectional process, whereby organisms evolve stem cells that are well-adapted to the characteristics of their microenvironment (including other cells, extracellular matrix, and the milieu of intercellular signaling molecules) and a tissue microenvironment that evolves to optimize stem cell performance (Fig. 12.1). While serving to improve body fitness and longevity, this coevolution of stem cells and tissue microenvironment should have important effects on selection within tissues and somatic evolution. To understand how evolution at the germline level (organismal evolution) impacts the character of somatic evolution in tissues, a brief summary of how selection at the germline level works in animal populations would be appropriate. Mutations are the ultimate source of genetic diversity in populations. Most mutations are known to have no or minimal effects on phenotype (neutral, or nonfunctional mutations), and of those that do have functional consequences (alter phenotype) most are known to be detrimental (Eyre-Walker and Keightley, 2007). Functional mutations often have well-defined, fixed phenotypic manifestations, such as by changing the color, shape, or quantity of a trait. However, the effects of such functional mutations on fitness are not an intrinsic property of genetic change, but are defined at the interface of phenotype and environment (Gorban et al., 2011; Orr, 2009). The white fur color of some hares is adaptive (increases fitness) in the presence of snow cover, but maladaptive (decreases fitness) in the absence of snow by making white hares more visible to predators. Selection can only act on genetic changes that have phenotypic manifestation and it is "blind" to neutral mutations. Although mutations that can improve fitness and promote selection favoring them are known to be rare relative to the frequency of neutral and detrimental mutations, they become even rarer as organisms become better adapted to their environments. In other words, as organisms adapt to external environments the rate and frequency at which they are evolving new adaptations decrease (a process known as *stabilizing selection*) (Silander et al., 2007; Smith, 1976). It is major changes in environments that can trigger a rapid evolution of the resident biota by increasing the frequency of mutations that are adaptive (which were much less frequent in the previously well-adapted state).

This general principle can provide important insights into why cancers, as a type of rapid somatic evolution, are mostly postponed to the later portions of the human lifespan. Moreover, the increased incidence of cancers universally scales to the later postreproductive portions of vastly different lifespans in different mammalian species. Based on the general evolutionary principle mentioned earlier, the coevolution of stem cells and tissue microenvironment that is driven by selection at the germline level for improved body fitness should in parallel reduce the probability of somatic mutations in stem cells that can improve their fitness at the somatic competition level. It is not clear so far if stem cells in young and healthy mammals are at their peak of adaptation to their niches in the tissue. However, both stem cells and tissue microenvironments within the reproductive portion of the lifespan (a young animal) are under the pressure of germline selection, while during the postreproductive ages their function is no longer shaped by germline selection to optimize tissue maintenance. This means that changes in tissue microenvironment that occur during the postreproductive portion of life are more impacted by random processes, and the degrading microenvironment does not represent an environment stem cells are adapted to by evolution at the germline level. Relaxation of the germline level selection at advanced ages thus leaves somatic evolution as the only means for stem cells to adapt to the age-altered microenvironment. Following current evolutionary theory, such changes should increase the frequency and adaptive value of a subset of mutations that did not confer adaptive benefits in the microenvironment of tissues within the reproductive portion of the lifespan. As oncogenic mutations are

typically functional mutations that have phenotypic manifestation, their positive fitness effects on stem cells capable of driving somatic evolution should increase in the postreproductive tissues relative to younger ages.

AGING AND SOMATIC EVOLUTION

For the last several decades, the link between aging and cancer has generally been recognized as aging representing the time necessary to accumulate oncogenic mutations in cells that drive carcinogenesis (Armitage, 1985; Armitage and Doll, 1954; Nowell, 1976; Vogelstein et al., 2013). Aging itself is often viewed in biomedical literature as primarily caused by the accumulation of mutations in cells which cause impaired cellular function (Lopez-Otin et al., 2013; Rossi et al., 2005). However, an increasing body of evidence demonstrates that the links between aging, mutations, and cancer are more complicated. This evidence indicates that the causative model "mutations cause aging and cancer" should be reconsidered, and the model "aging together with mutations promotes cancer" appears more plausible. It is important to distinguish the *time* component of aging from the *functional* component of aging, as there is not a linear association of the two. First of all, there is a marked discrepancy in how aging is explained in biomedical and evolutionary literature. Evolutionary models of aging suggest that longevity is an evolved process, and aging is dramatically promoted after the reproductive period or a period past which an individual of a particular species is unlikely to survive (Fabian and Flatt, 2011; Kirkwood, 2005). The prevailing evidence demonstrates that during the reproductive period of lifespan, selection for high body fitness postpones aging, likely through mechanisms of investing in tissue maintenance. Thus, functional decline with aging does not simply result from the passage of time, but is largely postponed to postreproductive periods by germline selection.

It has long been assumed that mutations accumulate linearly with age and cause a gradual body fitness decline. However, a sound body of evidence from mice and humans demonstrates that 40−50% of all mutations and epigenetic changes in the body accumulate before maturity when body growth stops (Horvath, 2013; Vijg et al., 2005). After this period, the accumulation of mutations markedly slows down, as the rate of cell divisions, particularly for stem cells, drops dramatically, as part of a switch from the developmental phase into a maintenance phase (Bowie et al., 2006; Sidorov et al., 2009). Still, the decline in body fitness does not follow this pattern and is postponed until middle to old ages. This delayed aging curve correlates with cancer incidence, and both are discrepant with the timing of the most intensive period of mutation accumulation. This evidence suggests that mutations alone are neither sufficient to cause aging nor cancer. The evolution of vastly different lifespans in mammals, often within close groups, corroborates this view in that within basically the same mutation rates and DNA maintenance machinery, evolution has been able to extensively modulate longevity in different mammal species. One excellent example for how quickly longevity can evolve comes from a study of Virginia opossums, *Didelphis virginiana*, which occur in eastern and southern parts of North America. Within just several 1000 years an insular population of the species, which experiences the absence of the mainland predators, has evolved a roughly 1.5 times reduced rate of aging (as evidenced by senescence in tissues) than the mainland populations (Austad, 1993). Reduced predation in its insular habitat promoted selection for delayed aging (functional decline), as this reduced predation presumably increased the odds of successful reproduction at ages where such success was much less likely on the mainland. On a broader scale, rodents represent a beautiful example of the evolution of vastly different lifespans and body sizes. Within one order *Rodentia*, species, such as the naked mole rat, *Heterocephalus glaber*, can live at least up to 30 years (Buffenstein and Jarvis, 2002), while the house mouse, *Mus musculus*, can only survive up to the max of 4 years in captivity. This evidence, alongside other such examples, demonstrates that the dynamics of aging is primarily determined by evolutionary forces acting at the germline level, depending on a particular species' population biology, but not by the characteristics of DNA maintenance machinery and mutation accumulation dynamics.

Similar to the delayed aging dynamics curve, most cancers are known to increase exponentially past the reproductive period. This association suggests that the aging process may have a direct causative effect on somatic evolution and cancer, rather than represent just the time factor for mutation accumulation. Multiple studies of the human hematopoietic system corroborate this idea. It has been shown that clonality in the hematopoietic stem cell compartment increases exponentially with age, being most rapid and profound during the postreproductive period (Genovese et al., 2014; Jacobs et al., 2012; Jaiswal et al., 2014; Laurie et al., 2012; McKerrell et al., 2015; Xie et al., 2014). The size and frequency of expanded large clones in hematopoietic stem cell system increase exponentially with age, with some clones occupying up to a third of the whole compartment, while early in life the clonal diversity generated by mutations is represented with a large number of clones of small size. This evidence is consistent with the idea that somatic evolution in general, beyond carcinogenesis, is promoted in advanced ages and suppressed earlier in life. This causative link between aging and somatic evolution is further corroborated by the evidence that longer lived laboratory mouse strains also demonstrate delayed cancer incidence relative to shorter-lived strains (Smith et al., 1973).

The mechanism for how aging can promote somatic evolution and cancer can be inferred from the mechanisms mentioned in the previous section. Relaxed selection for body fitness at the germline level during the post-reproductive period causes reduced investment in tissue maintenance and degradation of tissue microenvironments. This degradation manifests in many ways, such as increased chronic inflammation and altered intercellular signaling, metabolite byproduct accumulation, fat accumulation, alterations in structural integrity, and other phenomena that lead to an altered state of tissue microenvironment. By this time, mutations that have accumulated create genetic and phenotypic diversity in the stem cell compartments. Early in life such diversity is mostly represented with neutral and maladaptive changes due to the coevolution of stem cells and tissue microenvironment which favors wild-type cell phenotype. However, in an altered microenvironment, normal wild-type stem cells are no longer as fit, and somatic evolution favors new cell phenotypes generated by somatic mutations. Unlike early in life, somatic evolution is the only means of adaptation to the niche for stem cells during the post-reproductive period.

It has long been assumed that oncogenic mutations that promote somatic evolution and carcinogenesis have immediate fixed fitness effects on stem and progenitor cells. Attempts have been made to measure this advantage for specific mutations (Bozic et al., 2010). However, multiple studies clearly demonstrate that oncogenic mutations have varying effects on stem cell fitness which depends on the context/microenvironment (Fleenor et al., 2010, 2014; Henry et al., 2010; Marusyk et al., 2009; Vermeulen et al., 2013). Many oncogenic mutations have been shown to promote somatic evolution only in altered microenvironments, such as those affected by inflammation, ionizing irradiation, or aging. And it is clear that a cell resistant to hypoxia (which often develops in tumors) or a certain drug, although being a fixed defined cellular phenotype, will only have selective advantage over other cells in presence of these environmental factors. As hypoxia or drug application can negatively affect other cells, the fitness advantage of the mutant resistant cell lines will be proportional to the severity of these environmental factors, and thus is not a stationary value. Following these examples, similar conclusions about physiological conditions can be made. In an aged, degraded tissue microenvironment not tuned by evolution at the germline level, the selective forces acting on somatic cells will be dramatically different from those acting during the reproductive period in an evolved tissue microenvironment. Why changing selective pressures acting on stem cells will inevitably follow changes in a tissue's physiological state and microenvironment stems from the very mechanism of how the phenomenon of fitness arises. Fig. 12.2A and B demonstrates a simple example with two hypothetical species of bacteria, whereby each species has different adaptation to two environmental factors: media acidity and oxygen concentration. As shown in Fig. 12.2C and D, it is not the genetic makeup of the species itself that defines its fitness in a multifactorial environment, but the interaction between the phenotype and particular states of the environment. Therefore, fitness is not a fixed property of genetic change and cannot be measured as a defined property characteristic of any particular oncogenic mutation in regard to the affected cells without considering external microenvironmental signaling cues that govern stem or progenitor cell fate decisions.

The character of somatic evolution early and late in life, on the other hand, may have important consequences for evolution at the organismal level. If high rates of clonal evolution in somatic tissues were equally likely early and late in life, mutations in the male germline stem cell (GSC) compartment could markedly affect organismal evolution. A mutant GSC clone that expands significantly increases the chances of inheritance of any mutation that occurs within it. Thus suppression of somatic evolution during the early and reproductive ages should be an important mechanism that minimizes the chances of inheritance of somatic mutations in GSC through the male lineage, which should be favored by selection at the organismal level. There are many reports that the risk of certain mutation-associated diseases, such as schizophrenia or autism, in children positively correlates with father's age, and more mutations are passed to progeny by aged fathers (Callaway, 2012; Kong et al., 2012). It is unclear so far if this association is a consequence solely of the accumulation of mutations in sperm cells or whether elevated rates of mutation-induced somatic evolution (clonal expansions of mutants) contribute to these statistics. Positive selection for mutant GSCs and their clonal expansion that ensues will greatly elevate the probability that the mutation is inherited by progeny. Indeed, positive selection in GSC is known to be responsible for higher rates of inheritance of one mutation in the *RET* proto-oncogene from older fathers (Choi et al., 2012). This mutation is causative of the syndrome called *multiple endocrine neoplasia* that precedes a highly aggressive thyroid cancer. As germline (spermatogonial) stem cells in humans divide relatively frequently (approximately every 16 days), mutation accumulation and mutation-driven somatic evolution should significantly elevate the rate of mutation inheritance over a lifetime if the fitness benefits of new mutations are not suppressed through typical reproductive ages by the mechanisms described earlier. Important questions remain: is competition in GSC pools more effective in early life but becomes less effective past ages when men were unlikely to be around to pass their genes on, at least for the majority of our evolutionary history? What would be the mechanism for selecting against GSCs that acquire potentially

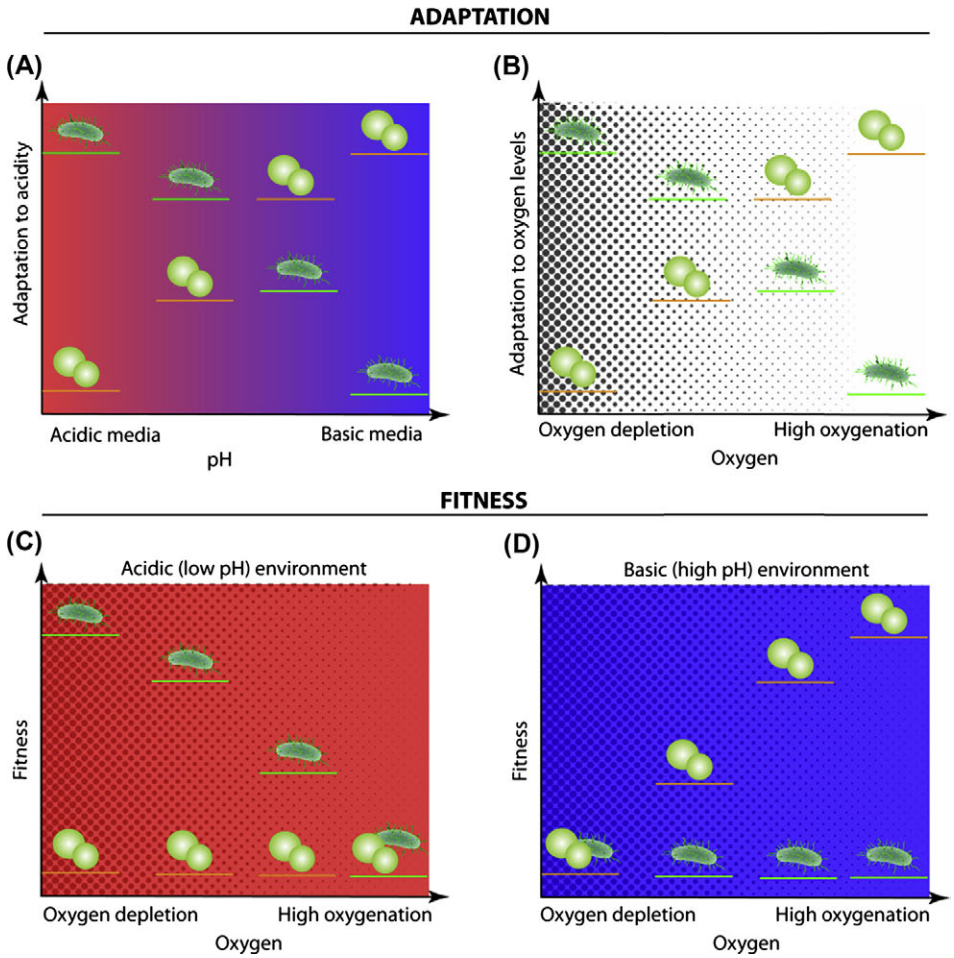

FIGURE 12.2 Fitness is an environment-dependent, dynamic property. Hypothetical ciliated bacterium and cocci demonstrate different tolerance to media acidity (A) and oxygen concentration in the media (B). Following the Sprengel-Liebig Law of the Minimum, organismal fitness is limited by the factor that the organism is worst adapted to, called the *limiting factor*. In a bifactorial environment, in acidic media (C), the ciliated bacteria's fitness will depend on oxygen concentration (the limiting factor), while the cocci's fitness will be low independent of the oxygen concentration as media acidity is the limiting factor for the cocci. In a basic bifactorial media (D), the limiting factors that determine fitness for the two species switch.

dangerous mutations, such as a mutation that could promote increased cancer risk if passed on to offspring?

Evidence presented thus far brings the theory of carcinogenesis in accord with evolutionary theory and strengthens the idea that aging is not only a factor associated with increased cancer incidence, but one that directly promotes carcinogenesis.

EVOLUTIONARY STRATEGIES FOR CANCER SUPPRESSION

Cancer is a malignant form of somatic evolution that often leads to death and thus lowers organismal fitness. Therefore selection during the evolutionary history of multicellular animals has acted to prevent cancer during the reproductive portions of a lifespan. Mammals have evolved some general cancer suppression mechanisms, and some of these mechanisms appear to be shared across metazoans. In addition, specialized group-specific strategies are known. Carcinogenesis is initiated by oncogenic mutations and epigenetic changes. However, its progression is a somatic evolutionary process which requires certain conditions. Under favorable conditions, oncogenic mutations drive clonal expansions of the recipient cell clones. By multiplying the initiated premalignant clonal context, clonal expansions dramatically increase the number of cells containing an initiating mutation, and thus proportionally increase the probability that another oncogenic mutation will happen within the effected clone. This process is thought to happen sequentially as other mutations promote such clonal evolution even further, leading to the formation of tumors. Typically a number of cancer driver mutations are necessary to make a stem or progenitor cell malignant, eventually leading to a cancer. Cancerous cells typically have several crucial characteristics that distinguish them from most healthy cells. First, cancerous cells are often capable of

uncontrolled and unlimited number of cell divisions and produce more progeny than normal cells (and that is why tumors form). Cancers can relinquish normal physiological constraints, including migration throughout the body and the establishment of new cancerous growths in other parts of the body, the process called *metastasis*.

If left untreated, cancer is typically a lethal disease and thus lowers the fitness of the affected individuals in animal populations, if occurring during the prereproductive or reproductive portion of the lifespan. Alterations in fitness inevitably alter selection acting on particular organisms, and thus cancer prevention, or suppression, during early portions of the lifespan must have evolved over evolutionary time, especially in large and long-lived animals such as mammals. It is now becoming clear that strategies to prevent cancer may differ in different mammals (Caulin and Maley, 2011), although common mechanisms related to the general evolution of multicellularity and lifespan are also active. Moreover, evidence indicates that limiting cancer is achieved by different means in different tissues of the body that differ in the organization of their stem and progenitor pools.

There are two major types of genes that are linked to cancer initiation and progression upon mutation or alteration in their expression: *oncogenes* and *tumor suppressor genes* (TSGs). Oncogenes typically are mutated to generate constitutively activated versions of *proto-oncogenes* which normally regulate important cellular functions, such as cell division; they promote cancer when hyperactivated, either by mutation of the coding sequence to increase activity (or remove control) or by overexpression (such as via promoter changes or by gene amplification). TSGs, on the other hand, prevent cells from becoming malignant. As already mentioned, the p53 protein produced in humans by the gene *TP53* (*Trp53* in mice) is an example of a TSG that directs mutant cells to a form of programmed cell death, *apoptosis* (among p53's many activities related to tumor suppression). TSGs often require inactivation of both alleles (two mutation hit model) to promote cancer. Therefore, the evolution of TSGs represents one of the cell-intrinsic evolutionary strategies to prevent cancer. Redundancy in the number or copy number of TSG has been suggested as one evolutionary strategy to prevent cancer in larger and longer lived animals (Caulin and Maley, 2011). For example, elephants have extra copies of the *TP53* homolog (Caulin et al., 2015; Caulin and Maley, 2011). Such multiplication of TSGs specifically in a particular species or genus would be an example of what we will call *boutique strategies* (for being specialized to particular groups of animals). More TSG copies or TSGs would necessitate more oncogenic mutations to make a cell malignant. There's evidence, for example, that more cell signaling pathways in which TSGs are involved need to be mutated in humans than in mice in at least some cell types (Rangarajan et al., 2004). Still, solid evidence that would support the evolution of TSG redundancy as a strategy to prevent cancer in a larger animal is still lacking. The rapidly increasing number of animal species for which whole-genome sequences are available now allows for a direct examination of this potential mechanism. If selection for multiple copies of TSGs is active in larger animals, then multiple TSGs with an open reading frame (intact coding sequence that suggests functional expression of the gene) should be found in their genomes. Basically, the extra TSGs should exhibit signatures of *purifying selection*, with continued conservation of coding sequence. Inactive copies with stop codons within the coding sequences (or changes in key residues), on the other hand, will indicate that such events of gene duplications were incidental, and only one copy is under purifying selection, which would oppose the idea of TSG multiplication as an anticancer strategy.

Maintenance of telomeres is another mechanism to limit the risk of cancer through reproductive years (Caulin and Maley, 2011). *Telomeres* are terminal parts of chromosomes. Telomeres shorten with each cell division, due to the requirement for templating during DNA replication. When this shortening reaches a certain threshold, the cell recognizes these ends as double-strand DNA breaks, which typically leads to cell elimination via apoptosis or senescence (the latter being a permanent exit from the cell cycle). An enzyme called *telomerase* is capable of protecting telomeres from shortening during cell division, and high expression in germline cells maintains telomere length from generation to generation of organisms. However, in mammalian tissues this enzyme is expressed only in stem and progenitor cells, and its expression is insufficient to completely prevent telomere attrition. Therefore the ability of stem cells to divide and self-renew is limited by the process called *replicative senescence*. This mechanism, thought to function as a "clock" to limit the number of cell divisions, likely represents an important evolved anticancer strategy. It has been proposed that shorter telomeres should have evolved in larger and longer lived animals as a strategy to reduce the increased risk postulated to be conferred by the greater number of cell divisions required for the development and maintenance of such animals. Indeed, telomerase activity has been found to negatively correlate with body size in rodents, although not with longevity (Seluanov et al., 2007). Comprehensive comparative studies, however, even within mammal taxa, are lacking, and the idea needs further investigation.

Above the intracellular level, the immune system has a role in cancer prevention by monitoring the body for cells expressing tumor-related markers on their surface and eliminating such cells. This process is called *immune*

surveillance (Kim et al., 2007; Vesely et al., 2011). Mice with deficiencies in both the adaptive (eg, T and B lymphocytes) and innate (eg, natural killer cells) immune system, for example, demonstrate significantly higher frequencies of spontaneous tumors, as well as tumors induced by carcinogens (Kim et al., 2007). Immune surveillance thus inhibits and delays the development of tumors and cancer. However, tumors are known to develop phenotypic diversity within their cellular population, and over time cells capable of escaping immune surveillance appear in a process called *immunoediting*. Successful cancers also sculpt their tumor microenvironment, such as by recruiting and supporting a type of macrophage that promotes cancer progression and inhibits immune elimination. Thus the immune system appears to be limited in its power to suppress cancer. Improved immune surveillance has been hypothesized to have evolved in larger, long-lived animals (Caulin and Maley, 2011), but evidence supporting the idea is currently lacking. Regardless, immunity is clearly a contributor to cancer prevention in mammals (and likely other animals).

Tissue maintenance has been proposed as another general anticancer mechanism (DeGregori, 2011, 2012). Evidence indicates that aging and tissue degradation is caused by systemic aging-related changes in tissue maintenance that operate above the cellular level, rather than by the accumulation of genetic damage in cells as believed previously (Austad, 1993; Kirkwood and Rose, 1991; Rozhok et al., 2014; Yuan et al., 2009). The already discussed rapid evolution of lifespan diversity within closely related groups indicates that the dynamics of aging and tissue fitness decline are highly pliable to selection at the germline level (Austad, 1993; Harrison and Roderick, 1997). The age-dependent incidence of cancers and other diseases appears to scale to lifespan as well. While mice develop cancers at increased frequency mostly after their first year of life (Pompei et al., 2001), in humans a similar pattern occurs roughly starting from age 45−50 years. A similar scaling to the end of the reproductive portion of life is known for cats and dogs (Vascellari et al., 2009). Also, longer lived laboratory strains of mice demonstrate delayed cancer incidence increase relative to their conspecifics, demonstrating a rapid evolution (with human-managed artificial selection in this case) of the age-dependent cancer incidence curve to scale to the extended lifespan. Additionally, there is experimental evidence demonstrating that oncogenic mutations are differentially selected in young and aged tissues (Henry et al., 2010, 2015; Vas et al., 2012a,b). Most of the typical oncogenic mutations, including those in the Ras, Myc, AKT, β-catenin, and other key cell signaling pathways, while positively regulating stem cell divisions rates, have been shown to decrease stem cell self-renewal by inducing higher rates of cell differentiation (DeGregori, 2012). This effect should cause the affected stem cells to leave the stem cell compartment and differentiate into tissue-specific cell types which have a limited lifespan. Thus, this mechanism should eliminate oncogenic mutations from the body. However, it has been shown that in aged or damaged tissue, such as those affected by inflammation or irradiation, oncogenic mutations can now confer selective advantages to stem cells relative to the rest of the stem cell compartment, leading to clonal evolution of premalignant clones and eventually to cancer (Bilousova et al., 2005; Fleenor et al., 2010, 2014; Henry et al., 2010; Marusyk et al., 2009, 2010; Vermeulen et al., 2013). Basically, aging or damage-induced reductions in the fitness of stem cells in a tissue create selective pressure for adaptive mutations (some of which can be oncogenic).

Thus, the dynamics of aging, which evolves at the germline level as part of the evolution of lifespan, is in itself a mechanism directly impacting cancer incidence. One of the best-known factors that promote carcinogenesis in an aging-dependent manner is chronic inflammation. Inflammation has been shown in multiple experiments to promote various cancers in different tissues and appears to be a universal procancer factor (Coussens and Werb, 2002; Hanahan and Weinberg, 2011; Vermeulen et al., 2013; Westphalen et al., 2014). Chronic inflammation is known to universally increase with aging and promote aging by damaging tissues and affecting the stem cell capability of tissue renewal. This process is so universal to mammals and other animals that there exists the term *inflammaging* referring to the tight link between inflammation and aging (Goto, 2008). Thus, as part of the aging process, inflammation is thought to be one of the factors associated with increased cancer rates in the elderly. In accord with this view, laboratory mice strains that demonstrate low inflammation profiles are also less prone to cancer. In humans, regular administration of nonsteroidal antiinflammatory drugs (NSAIDs), such as aspirin, is known to associate with reduced cancer risk, in some cases eliminating as much as 40% of the risk for particular cancers (Rostom et al., 2007). Inflammation may itself result from tissue breakdown during the aging process, such as following loss of effective barrier function in the intestinal tract (leading to infiltration of bacteria and their products). Thus, while inflammation is a highly beneficial program for combating infections and repairing damaged tissue (explaining the strong selective pressure underlying its evolution), it can promote diseases including cancer late in human life (largely beyond reproductive periods influenced by natural selection).

Additional cellular and systemic mechanisms, such as those controlling mTOR signaling (Guertin and Sabatini, 2007) and autophagy (Rosenfeldt and Ryan, 2009), are also key modulators of aging and carcinogenesis, indicating that aging is not only associated with higher cancer rates as a

time factor needed for mutation accumulation, but is a direct cancer-promoting agent altering selective pressures acting on the genetic diversity of dividing cells in the body. This view suggests that practices that help maintain higher body fitness are capable of providing an additional cancer suppressive mechanism by inhibiting the previously mentioned procancer aging-related processes in the body. Indeed, lifespan-extending/cancer reducing practices such as caloric restriction and exercise are known to promote autophagy and reduce chronic inflammation, which should contribute to prolonged tissue maintenance (and thus delayed promotion of oncogenic adaptation).

The diversity of cancer-suppressing mechanisms among various groups of mammals is still poorly understood. Open questions exist as to why longer lived and larger mammals, sometimes differing seven orders of magnitude in size and up to 100-fold in lifespan, such as whales and mice, demonstrate similar avoidance of cancer during their natural lifespans (the period when survival is likely in the environments in which they evolved). This question is known as *Peto's paradox*. Intuitively, larger animals have more stem and progenitor cells that represent a larger target pool for oncogenic mutations. Longer lifespans also provide more cell divisions for the mutations to accumulate. So far most cancer models have been primarily focused on the occurrence of mutations, assuming that each oncogenic mutation immediately and inevitably leads to clonal proliferation and is thus rate-limiting for cancer progression. From the standpoint of this paradigm it is indeed puzzling why whales are not more prone to cancer than mice. Hence, the paradox was formulated. However, the mechanisms and evidence discussed above in this chapter, as well as an improved evolutionary understanding of cancer suggest that carcinogenesis is not just a succession of mutations, but rather is a complex somatic evolutionary process that is regulated above the cellular level. When the dynamic evolutionary concept of fitness is incorporated in the cancer model, then cancer progression, as a type of somatic evolution, can primarily be understood as an environment-dependent process. At the organismal level, it is major environmental perturbations that lead to rapid evolution as organisms try to adapt to the new environment. As a population adapts to a particular environment, its evolution slows down. Basically, once a population of organisms is well adapted to their environment, stabilizing selection favoring the status quo becomes more dominant (purifying selection, which removes mutations reducing organismal fitness, will be dominant over positive selection). A similar process should hold for stem cells and their clonal evolution. Thus, somatic evolution and cancer should be promoted in aged tissues as the primary means of cellular adaptation to the altered, nonoptimal environment. This view of cancer can resolve Peto's paradox regarding the differences in lifespan among mammals. The power of stabilizing selection that suppresses clonal evolution in animal tissues should be proportional to the pool sizes of stem and progenitor cells, as it is in organismal populations, and thus dictates that an oncogenic cell in the large tissue of a whale has a lower capability to overcome competition with the large number of nonaffected cells than it would have in a mouse tissue. Such stabilizing selection could counteract the increased risk of occurrence of oncogenic mutations due to larger tissues and longer lives (and thus, a greater number of cell divisions).

Alongside the general cancer suppression mechanisms described previously, additional specialized species/group-specific cancer prevention strategies are known in some mammals. As already mentioned, in rodents the activity of telomerase negatively correlates with body mass (Seluanov et al., 2007). Thus in larger rodents, as shown for fibroblast cells, telomerase activity is repressed and the cells undergo replicative senescence after a number of cell divisions, which incapacitates their ability to divide and accumulate oncogenic mutations. However, no correlation with lifespan has been found. It has been shown, however, that among small rodents, in which telomerase is active and cells do not undergo replicative senescence, long-lived species exhibit slower cell division rates. Consistent with these observations, stem cells from humans are also known to have lower division frequencies relative to their murine counterparts. Thus slower stem cell division rates could represent a mechanism ensuring lower risk of oncogenic mutations in long-lived species.

A species with an exceptionally long lifespan among rodents, the naked mole rat, can live over 30 years (Buffenstein and Jarvis, 2002) and appears to be resistant to cancers, as no cancer incidence has been observed (Tian et al., 2013). It should be noted, however, that cancer appears to be rare in most if not all species *in the wild*, as natural selection has limited cancer to periods of life when an individual was unlikely to survive and thus reproduce. Most humans and of course laboratory mice, in which cancers and aging are largely studied, are no longer "in the wild." Captivity or life in protection from natural hazards markedly affects a species' survival curve as shown in (Fig. 12.3) in that it is only under such conditions that survival is limited by the species' maximum physiological lifespan. As shown in Fig. 12.3A, cancer incidence to a large extent mirrors the physiological decline (for which survival curves are a good indication in protected conditions). Likewise, mouse strains of different longevity demonstrate corresponding cancer incidence frequency "adjustments" that scale cancer incidence to the changes in the lifespan that have happened with the strain as a result of selection in captivity (Fig. 12.3B). Thus, a simple explanation of the rare occurrence of cancer in wild animals can be that they simply do not survive to the age at which senescence promotes cancer or other

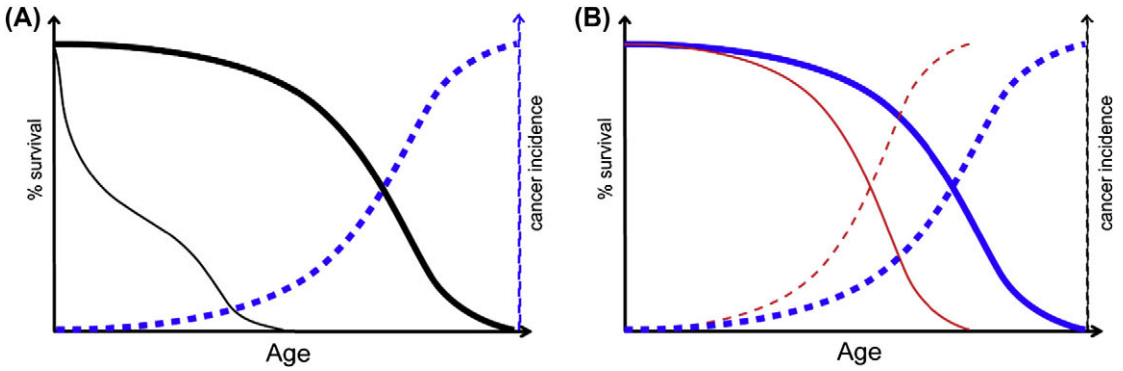

FIGURE 12.3 Survival curves for wild and protected/captive animals differ. (A) Survival curves for wild (*thin black line*) and captive (*thick black line*) animals differ; cancer incidence (*dashed blue line*) mirrors the extended lifespan of humans and captive animals. (B) Survival/longevity profiles (*solid lines*) of different laboratory mouse strains (*colors*) incur corresponding changes in cancer incidence (*dashed lines*).

diseases. Over half a century ago, the "father of transplantation" Peter Medawar was among the first to propose this explanation in his famous 1951 lecture at University College London:

> *Animals do not in fact live long enough in the wild to disclose the senile changes that can be made apparent by their domestication… It is of vital importance to remember that senility is in a real and important sense an artifact of domestication; that is, something revealed and made manifest only by the most unnatural experiment of prolonging an animal's life by sheltering it from the hazards of its ordinary existence.*

From this perspective, the longevity and cancer resistance of naked mole rats may not really be "exceptional," in that investigators have not followed sufficient numbers of animals to ages much beyond the lifespans observed in the wild. Nonetheless, fibroblasts of this species have been shown to secrete a unique form of the molecule *hyaluronan*, a major component of the extracellular matrix in many tissues that is important to cell proliferation and migration (Tian et al., 2013). Their hyaluronan has a larger molecular weight compared to humans and mice and accumulates abundantly in tissues throughout the body. The cells of this species are also more sensitive to hyaluronan-induced signaling. While the naked mole rats do not appear to develop cancer during their natural lifespans, perturbations in hyaluronan signaling have been shown to make normally transformation-resistant fibroblasts pliable for malignant transformation. The high molecular mass hyaluronan of the naked mole rat has been found to increase the cells' response to *contact inhibition*—a mechanism that arrests cell division in animal cells upon contact with other cells. Tumor cells escape this inhibition and thus can grow in an uncontrolled manner. It is thus believed that the naked mole rats have evolved a modified version of hyaluronan as one cancer protective mechanism that is specific (and perhaps unique) to this group.

Another distinctive trait is that typical signs of aging have not been observed in the naked mole rats, and in captivity they remain fit and healthy well into their third decade of life, maintaining high reproductive capability (Buffenstein, 2008). The relative lack of predators and other external hazards in their sealed underground burrows likely facilitated the evolution of long life in these mole rats, as the investment in tissue maintenance for several decades could be rewarded by successful reproduction. The vast majority of deaths observed in captivity are from fights between individuals for dominance in the social hierarchy. Therefore, the true potential lifespan of the species is probably underestimated. From this perspective the absence of observed cancers in naked mole rats may also stem from their retarded aging within at least three decades of life, which may be tumor suppressive as a general strategy whereby selection at the germline level acts to suppress cancer and fitness decline within reproductive years. It might well be that in their natural environment fights for social dominance is a major cause of deaths in the naked mole rat. This could also be a possible explanation of their longevity, as it would create a positive selective pressure on late-life physical fitness.

A multitude of other group-specific cancer preventive mechanisms could have evolved in different mammals, and studies of these mechanisms could reveal novel tumor suppressive strategies that could be applied to humans, even when humans did not evolve these same mechanisms. Alternatively, group-specific mechanisms might turn out to be rare at least among mammals, given that the same evolutionary strategic "task" (cancer avoidance) operates within what is principally the same physiologic system.

TISSUE ORGANIZATION AND TUMOR SUPPRESSION

The character of somatic evolution, and thus the evolutionary forces that determine progression toward cancer,

differ in different tissues of the body. The underlying stem and progenitor cell pools are organized in a tissue-specific manner, and the spatial architecture of stem and progenitor pools and their function is believed to have been part of anticancer strategies in animal evolution. For example, from the standpoint of somatic selection, hematopoietic stem cells (HSCs) represent effectively one large population competing for the limited niche space of the bone marrow (Abkowitz et al., 1996; Catlin et al., 2011; Wright et al., 2001). The size of the HSC pool, according to various estimates, totals from 11,000 to ≈300,000 cells in the adult human body (Abkowitz et al., 2002; Wang et al., 1997). HSCs are spatially separated from each other and their competition is thought to be realized in their differential proclivity to divide, die, senesce, or differentiate. HSCs are known to migrate to different parts of the body through the blood stream and return to their bone marrow niches with certain frequency, setting up what resembles the game of musical chairs (each division and migration comes with a risk of losing one's niche). Similar organization and properties appear to be true for mesenchymal stem cells that give rise to a variety of specialized cells contributing to the bone, cartilage, muscle, and other tissues. These large effective population sizes and competition structures are conducive to various forms of selection. As already mentioned, significant changes in clonal frequencies and massive expansions of certain HSC clones within the HSC compartment are known to occur with age (Genovese et al., 2014; Jaiswal et al., 2014; McKerrell et al., 2015; Xie et al., 2014).

On the other hand, animal epithelia are organized in a different way. These are compartmentalized into small replicative units with a limited number of stem cells physically confined into small niches. For example, gut epithelial stem cells are separated into *crypts*, tiny invaginations of the gut epithelium that contain on the order of 15−20 stem cells. Such segregation leads to a multitude of small stem cell populations for which competition is mostly limited to that occurring within crypts (Fig. 12.4). Such a small effective population size leads to substantially weakened selection and increased drift (random changes in clonal frequencies). And gut epithelia stem cell clones have actually been shown in multiple studies to follow the drift-dominated scenario (Lopez-Garcia et al., 2010; Snippert et al., 2010; Vermeulen et al., 2013). Such architecture might be a powerful cancer suppressive mechanism. Epithelia, and the gut surface in particular, increase enormously with increased body size, representing increased target size for oncogenic mutations. It has been shown in mice, however, that some typical oncogenic mutations, such as in *TRP53*, *Kras*, and *Apc* genes, do not give a robust selective advantage in intestinal stem cell pools and their fate is significantly influenced by drift. Such mutant cells are often replaced by normal stem cells in intestinal crypts. This small population size and the domination of drift in clonal dynamics should prevent early premalignant cells that contain oncogenic mutations from expanding in the stem cell compartment. While an oncogenic mutation could be fixed within a crypt-limited stem cell pool by chance alone (and perhaps amplified by positive selection),

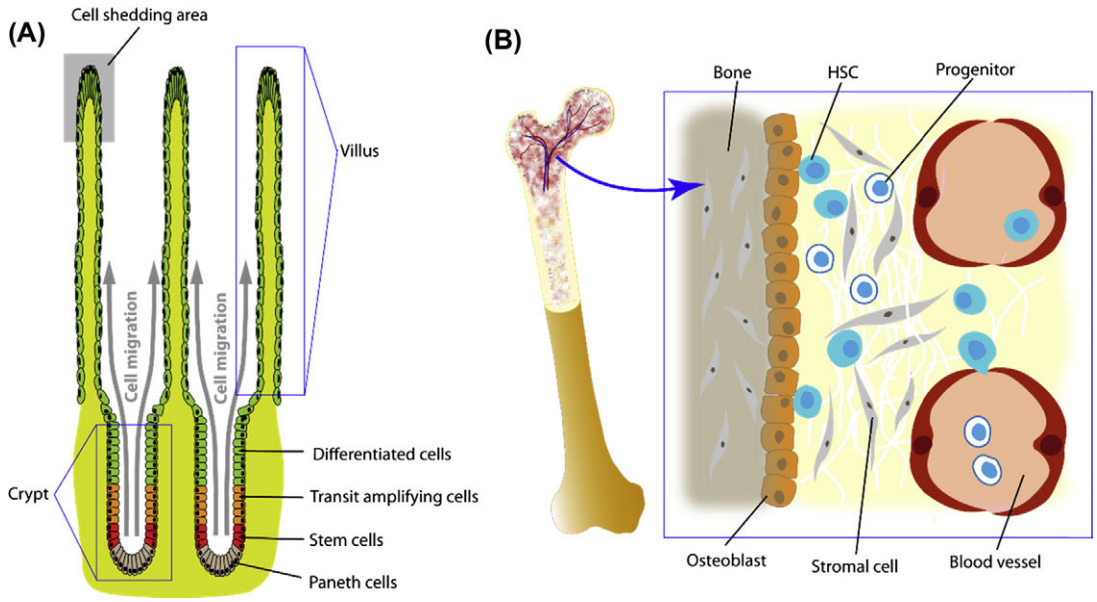

FIGURE 12.4 Stem cell pools for different tissues have different structural organization. (A) Intestinal epithelial stem cells are segregated in small clusters of 15−20 cells per crypt; clonal dynamics within each crypt are dominated by random drift. (B) hematopoietic stem cells (HSCs) of the bone marrow compete as one large population and can migrate to other parts of the hematopoietic tissue in the body via blood vessels; clonal dynamics in HSC are stronger, affected by selection.

this clone would still be of limited size (15−20 cells). As already mentioned, expansions of oncogenically initiated clones have a dramatic effect on the probability of accumulating several oncogenic mutations in one clonal context and are thus a critical rate-limiting step in cancer development.

It is not clearly understood so far if such differences in tissue organization have been part of cancer prevention strategies during animal evolution. HSC population size does not appear to scale with body size, as cats appear to have similar numbers of HSC as mice, and humans may have similar to not much more than 10-fold more HSC (Abkowitz et al., 2002). Thus, one evolved mechanism for tumor suppression with larger body size would be to simply limit the increase in stem cell number (a key target of oncogenesis). On the other hand, the size of epithelia populations for tissues such as skin and the gut should be proportional to body size, and given the segmental organization of epithelial stem cell pools, these numbers should relatively scale with body size. Between a whale and a mouse this difference is seven orders of magnitude (in weight and presumably in cell numbers). Such a dramatic increase in the target size for oncogenic mutations in epithelia could have required a different stem cell organization that would prevent clonal evolution. Interestingly, hematopoietic cancers are more prevalent than carcinomas (epithelial cancers) in mice, but in humans the opposite is true. This epidemiology is consistent with the idea that the difference in the target size for oncogenic mutations between human and mice epithelia is greater than that for hematopoietic cells. Based on the structure of HSC and epithelial stem cell pools, we would also predict that the former should be more sensitive to smaller phenotypic effects of mutations, while effective selection (whether purifying or positive) within the latter should require greater phenotypic effects.

EVOLUTIONARY UNDERSTANDING OF CANCER: AN IMMINENT PARADIGM SHIFT

Cancer is a major cause of human deaths worldwide. Most cancers generally follow an exponential increase with age, being prevalent mostly during the postreproductive period of the lifespan. Thus aging is the most straightforward risk factor for cancer. However, some specific types of cancer disobey this pattern. The incidence of testicular cancer is mostly concentrated within the reproductive portion of life, when spermatogenic cells are most active. Bone cancers, in addition to late-life increase, also have a substantial peak of incidence during early ages when the skeleton is growing. Moreover, the natural incidence of cancers can be substantially modulated by environmental cancer risk factors. Exposure to carcinogens like radiation and benzene, smoking, alcohol abuse, and obesity are among the many factors linked with elevated cancer risk. Changes in the modern lifestyle can have dramatic impacts on some cancers as well. For example, breast cancer is very rare in primitive tribal communities but is among the most common cancers in modern women. Such an increase is explained by a substantial role of hormones in breast cancer etiology. Women with suppressed menstrual cycles, such as by pregnancy and lactation, are thought to be under lower risk, and the frequency of pregnancy per lifespan and the length of nursing per child has dramatically decreased with the development of modern society. Beyond such specific examples, however, cancer is generally thought to be rate-limited by the occurrence of oncogenic mutations in cells. Most cancers require several such mutations to produce a malignant cell. Therefore, factors such as exposure to carcinogens or smoking are thought to promote cancer primarily by inducing more mutations, including oncogenic ones. As described previously, aging is thought to be associated with increased cancer risk primarily as the time factor needed for more mutations to accumulate. However, increasing evidence has been emerging over the last decades indicating that the relationship between aging, somatic evolution, and cancer is more intricate than previously believed. An increasing body of evidence indicates that it is not the occurrence of oncogenic mutations per se, but changing, context-dependent somatic evolutionary forces determining the fate of these mutations that are the primary rate-limiting mechanism for cancer.

The prevailing explanation of human age-dependent cancer incidence, which has been around since the 1950s, assumes that mutations accumulate linearly with age, and oncogenic mutations drive clonal proliferation of the recipient cells. As oncogenically initiated clones expand and become represented with more dividing cells, they increase the likelihood that other oncogenic mutations will happen within the same clonal context. Over time, this process is supposed to promote the accumulation of multiple cancer driver mutations in one cell clone, which results in a malignant cell clone that leads to cancer. As the frequency of such cells (and thus cancer) is supposed to increase linearly with age, the number of such mutations has been inferred from the exponential curve of cancer incidence, assuming that each oncogenic mutation in a sequence adds a certain fitness advantage to the recipient cell. The impact of this paradigm on the investment of effort and money in cancer research is clear; for example, despite the fact that cancer is largely a disease of old age, almost all cancer modeling in mice employs only young mice (based on the mutation centric view, providing the oncogenic mutations should suffice to understand cancer). But as we have argued, the age of the host really does matter. Moreover, the cataloging of cancer mutations across thousands of human cancers through genome sequencing

for The Cancer Genome Atlas (TCGA) project has required hundreds of millions of dollars of National Institutes of Health research funds, and has largely been driven by the view that understanding the constituent drivers will be key to understanding the cancer. Finally, most studies of cancer prevention focus on how the intervention impacts the developing cancer cells and most therapies target the cancer cells; these strategies largely overlook the tissue microenvironment, with notable exceptions, such as the explosion in the development of immune modulatory therapies (Joyce and Pollard, 2009).

However, evidence clearly indicates that almost half of all mutations and epigenetic changes (including oncogenic events) accumulate early (before age 20 years) during development and body growth, and the occurrence of all these forms of genetic damage dramatically slows down thereafter. This pattern is caused by a significant slowdown in stem cell division rates after body maturation. Therefore, the frequency of oncogenic initiation within cells in tissues should follow a similar pattern. But most cancers are extremely rare before age 20 years, and their incidence is still low until age 45 years. Moreover, it is now well appreciated that oncogenic mutations and microtumors are indeed very common in normal human tissue even through young ages (DeGregori, 2012; Martincorena et al., 2015), corroborating the idea that a substantial portion of oncogenic mutations do happen early, consistent with the general mutation accumulation pattern. However, these oncogenically initiated cells and microtumors rarely lead to cancer, suggesting that their progression is dictated by external factors.

The idea of a simple mechanistic explanation of cancer progression as solely determined by the constant positive fitness effects of oncogenic mutations thus fails to explain this discrepancy, just as it fails to explain the Peto's paradox and scaling of cancer incidence to different mammalian lifespans. And the current paradigm of cancer, being primarily centered on mutation occurrence, suffers from not considering key aspects of somatic evolution—the factors that determine the fate of somatic (including oncogenic) mutations. The key problem of early cancer modeling (including recent modeling), in addition to the assumption of linear mutation accumulation, has been the idea of a fixed fitness effect of somatic mutations on stem and progenitor cells. While mutations often have defined phenotypic effects on cells and organisms, their fitness effect is a dynamic property, which is determined at the interface of a phenotype and its environment. The magnitude of fitness effects of mutations is thus not a stationary parameter, but depends on external environment. If a cell acquires a hypoxia or drug resistance mutation, this defined phenotype will have no fitness advantage under normoxic tissue conditions or in the absence of the drug, respectively, while in a hypoxic tumor tissue of a tumor or under drug application the mutated cells will enjoy an advantage over nonmutant cells. Moreover, this advantage is not a stationary value as well, as it will increase proportionally as the conditions become more severe. In the complex tissue microenvironment, many such factors exist that affect signaling and cell fate decisions, and tissue microenvironment is known to degrade with age. During reproductive years, tissue maintenance is selected at the germline level and tissue microenvironment is thus kept relatively stable. Stem cells evolve at the germline level to optimally function in this environment; as part of their adaptation, germline selection should lead to increases in their fitness at the somatic level to prevent somatic evolution and cancer. This coevolution and the relative stability of tissue microenvironments provide a very different evolutionary landscape compared to older ages, for which germline selection is no longer active to support the evolved state. Therefore, in late life, somatic evolution is the only means of stem cell adaptation to tissue microenvironment. As the rates of aging accelerate during postreproductive years, so too should the rates of somatic evolution in response to these changes. And we know now that this scenario takes place indeed, at least in some tissues, and changes in clonal diversity and rapid clonal expansions, which are not typical in early life, occur in old age as a result of the increased fitness value of functional somatic mutations (Genovese et al., 2014; Jaiswal et al., 2014; McKerrell et al., 2015; Xie et al., 2014).

Another interesting question is how cancer risk-associated factors increase cancer incidence. While it is traditionally thought that carcinogens promote mutation accumulation and thus the occurrence of oncogenic mutations, this may be only part of the story. Insults, such as smoking and irradiation do induce mutations, but these factors also dramatically alter tissue microenvironments, including by causing severe damage and by elevating inflammation. Inflammation is also known to be induced by excessive alcohol consumption and obesity, which are also among factors that elevate cancer risk. So factors, such as carcinogens and radiation, do not only induce mutations, they also change tissue microenvironment in a way that should be conducive to clonal evolution.

Therefore, a body of new knowledge and evidence indicates that carcinogenesis, just like somatic evolution in general, is likely to be a process that follows the same evolutionary principles known from organismal biology. It starts with the occurrence of functional mutations in competitive stem and progenitor cell populations, which generates phenotypic diversity. This increasing diversity is subject to the balance of stabilizing and positive selection, which is primarily defined by the amount of alteration of the tissue microenvironment compared to its evolved state, which is maintained relatively stable during the reproductive portion of the lifespan and degrades thereafter. This degradation, analogous to that for natural ecosystems,

reduces stabilizing selection and promotes positive selection for a subset of the accumulated phenotypic diversity as a means of stem cell adaptation to a new environment. Somatic evolution, as we now know, is also subject to population size-induced drift, as shown for intestinal epithelia, which is likely one of the cancer preventive mechanisms harnessed by the evolution of long-lived, large multicellular animals. Other extrinsic factors, such as immune surveillance, likely also change with age and contribute to late-life cancer development. Thus, our understanding of the factors that govern the fate of somatic mutations in animal tissues will hopefully help merge cancer and evolutionary theories in a model of cancer that would be able to explain the many unexplained phenomena and paradoxes of cancer biology mentioned above, and to understand better the phenomenon of somatic evolution and its interaction with evolution at the organismal level.

REFERENCES

Abkowitz, J.L., Catlin, S.N., Guttorp, P., 1996. Evidence that hematopoiesis may be a stochastic process in vivo. Nature Medicine 2, 190–197.

Abkowitz, J.L., Catlin, S.N., McCallie, M.T., Guttorp, P., 2002. Evidence that the number of hematopoietic stem cells per animal is conserved in mammals. Blood 100, 2665–2667.

Alsberg, E., von Recum, H.A., Mahoney, M.J., 2006. Environmental cues to guide stem cell fate decision for tissue engineering applications. Expert Opinion on Biological Therapy 6, 847–866.

Armitage, P., Doll, R., 1954. The age distribution of cancer and a multistage theory of carcinogenesis. British Journal of Cancer 8, 1–12.

Armitage, P., 1985. Multistage models of carcinogenesis. Environmental Health Perspectives 63, 195–201.

Austad, S.N., 1993. Retarded senescence in an insular population of virginia opossums (*Didelphis virginiana*). Journal of Zoology 229, 695–708.

Bilousova, G., Marusyk, A., Porter, C.C., Cardiff, R.D., DeGregori, J., 2005. Impaired DNA replication within progenitor cell pools promotes leukemogenesis. PLoS Biology 3, 2135–2147.

Bissell, M.J., Hines, W.C., 2011. Why don't we get more cancer? A proposed role of the microenvironment in restraining cancer progression. Nature Medicine 17, 320–329.

Bowie, M.B., McKnight, K.D., Kent, D.G., McCaffrey, L., Hoodless, P.A., Eaves, C.J., 2006. Hematopoietic stem cells proliferate until after birth and show a reversible phase-specific engraftment defect. Journal of Clinical Investigation 116, 2808–2816.

Bozic, I., Antal, T., Ohtsuki, H., Carter, H., Kim, D., Chen, S., Karchin, R., Kinzler, K.W., Vogelstein, B., Nowak, M.A., 2010. Accumulation of driver and passenger mutations during tumor progression. Proceedings of the National Academy of Sciences of the United States of America 107, 18545–18550.

Buffenstein, R., Jarvis, J.U., 2002. The naked mole rat—a new record for the oldest living rodent. Science of Aging Knowledge Environment 2002, pe7.

Buffenstein, R., 2008. Negligible senescence in the longest living rodent, the naked mole-rat: insights from a successfully aging species. Journal of Comparative Physiology B 178, 439–445.

Callaway, E., 2012. Fathers bequeath more mutations as they age. Nature 488, 439.

Catlin, S.N., Busque, L., Gale, R.E., Guttorp, P., Abkowitz, J.L., 2011. The replication rate of human hematopoietic stem cells in vivo. Blood 117, 4460–4466.

Caulin, A.F., Maley, C.C., 2011. Peto's Paradox: evolution's prescription for cancer prevention. Trends in Ecology and Evolution 26, 175–182.

Caulin, A.F., Graham, T.A., Wang, L.S., Maley, C.C., 2015. Solutions to Peto's paradox revealed by mathematical modelling and cross-species cancer gene analysis. Philosophical Transactions of the Royal Society London Series B 370.

Choi, S.K., Yoon, S.R., Calabrese, P., Arnheim, N., 2012. Positive selection for new disease mutations in the human germline: evidence from the heritable cancer syndrome multiple endocrine neoplasia type 2B. PLoS Genetics 8, e1002420.

Coussens, L.M., Werb, Z., 2002. Inflammation and cancer. Nature 420, 860–867.

DeGregori, J., 2011. Evolved tumor suppression: why are we so good at not getting cancer? Cancer Research 71, 3739–3744.

DeGregori, J., 2012. Challenging the axiom: does the occurrence of oncogenic mutations truly limit cancer development with age? Oncogene 32, 1869–1875.

Eyre-Walker, A., Keightley, P.D., 2007. The distribution of fitness effects of new mutations. Nature Reviews Genetics 8, 610–618.

Fabian, D., Flatt, T., 2011. The evolution of aging. National Education Knowledge 3, 9.

Fleenor, C.J., Marusyk, A., DeGregori, J., 2010. Ionizing radiation and hematopoietic malignancies: altering the adaptive landscape. Cell Cycle 9, 3005–3011.

Fleenor, C.J., Rozhok, A.I., Zaberezhnyy, V., Mathew, D., Kim, J., Tan, A., Bernstein, I.D., DeGregori, J., 2014. Contrasting roles for C/EBPalpha and notch in irradiation-induced multipotent hematopoietic progenitor cell defects. Stem Cells 33 (4), 1345–1358.

Ford, A.M., Mansur, M.B., Furness, C.L., van Delft, F.W., Okamura, J., Suzuki, T., Kobayashi, H., Kaneko, Y., Greaves, M., 2015. Protracted dormancy of pre-leukaemic stem cells. Leukemia 29 (11), 2202–2207.

Gatenby, R.A., Vincent, T.L., 2003. An evolutionary model of carcinogenesis. Cancer Research 63, 6212–6220.

Genovese, G., Kahler, A.K., Handsaker, R.E., Lindberg, J., Rose, S.A., Bakhoum, S.F., Chambert, K., Mick, E., Neale, B.M., Fromer, M., et al., 2014. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. The New England Journal of Medicine 371, 2477–2487.

Glick, D., Barth, S., Macleod, K.F., 2010. Autophagy: cellular and molecular mechanisms. Journal of Pathology 221, 3–12.

Gorban, A.N., Pokidysheva, L.I., Smirnova, E.V., Tyukina, T.A., 2011. Law of the minimum paradoxes. Bulletin of Mathematical Biology 73, 2013–2044.

Goto, M., 2008. Inflammaging (inflammation + aging): a driving force for human aging based on an evolutionarily antagonistic pleiotropy theory? Bioscience Trends 2, 218–230.

Guertin, D.A., Sabatini, D.M., 2007. Defining the role of mTOR in cancer. Cancer Cell 12, 9–22.

Hanahan, D., Weinberg, R.A., 2011. Hallmarks of cancer: the next generation. Cell 144, 646–674.

Harrison, D.E., Roderick, T.H., 1997. Selection for maximum longevity in mice. Experimental Gerontology 32, 65–78.

He, C., Bassik, M.C., Moresi, V., Sun, K., Wei, Y., Zou, Z., An, Z., Loh, J., Fisher, J., Sun, Q., et al., 2012. Exercise-induced BCL2-regulated autophagy is required for muscle glucose homeostasis. Nature 481, 511–515.

Henry, C.J., Marusyk, A., Zaberezhnyy, V., Adane, B., DeGregori, J., 2010. Declining lymphoid progenitor fitness promotes aging-associated leukemogenesis. Proceedings of the National Academy of Sciences of the United States of America 107, 21713–21718.

Henry, C.J., Casas-Selves, M., Kim, J., Zaberezhnyy, V., Aghili, L., Daniel, A.E., Jimenez, L., Azam, T., McNamee, E.N., Clambey, E.T., et al., 2015. Aging-associated inflammation promotes selection for adaptive oncogenic events in B cell progenitors. Journal of Clinical Investigation 125, 4666–4680.

Horvath, S., 2013. DNA methylation age of human tissues and cell types. Genome Biology 14, R115.

Jacobs, K.B., Yeager, M., Zhou, W., Wacholder, S., Wang, Z., Rodriguez-Santiago, B., Hutchinson, A., Deng, X., Liu, C., Horner, M.J., et al., 2012. Detectable clonal mosaicism and its relationship to aging and cancer. Nature Genetics 44, 651–658.

Jaiswal, S., Fontanillas, P., Flannick, J., Manning, A., Grauman, P.V., Mar, B.G., Lindsley, R.C., Mermel, C.H., Burtt, N., Chavez, A., et al., 2014. Age-related clonal hematopoiesis associated with adverse outcomes. The New England Journal of Medicine 371, 2488–2498.

Joyce, J.A., Pollard, J.W., 2009. Microenvironmental regulation of metastasis. Nature Reviews Cancer 9, 239–252.

Kim, R., Emi, M., Tanabe, K., 2007. Cancer immunoediting from immune surveillance to immune escape. Immunology 121, 1–14.

Kirkwood, T.B., Rose, M.R., 1991. Evolution of senescence: late survival sacrificed for reproduction. Philosophical Transactions of the Royal Society London Series B 332, 15–24.

Kirkwood, T.B., 2005. Understanding the odd science of aging. Cell 120, 437–447.

Klein, A.M., Simons, B.D., 2011. Universal patterns of stem cell fate in cycling adult tissues. Development 138, 3103–3111.

Kong, A., Frigge, M.L., Masson, G., Besenbacher, S., Sulem, P., Magnusson, G., Gudjonsson, S.A., Sigurdsson, A., Jonasdottir, A., Wong, W.S., et al., 2012. Rate of de novo mutations and the importance of father's age to disease risk. Nature 488, 471–475.

Laurie, C.C., Laurie, C.A., Rice, K., Doheny, K.F., Zelnick, L.R., McHugh, C.P., Ling, H., Hetrick, K.N., Pugh, E.W., Amos, C., et al., 2012. Detectable clonal mosaicism from birth to old age and its relationship to cancer. Nature Genetics 44, 642–650.

Li, L., Xie, T., 2005. Stem cell niche: structure and function. Annual Review of Cell and Developmental Biology 21, 605–631.

Lopez-Garcia, C., Klein, A.M., Simons, B.D., Winton, D.J., 2010. Intestinal stem cell replacement follows a pattern of neutral drift. Science 330, 822–825.

Lopez-Otin, C., Blasco, M.A., Partridge, L., Serrano, M., Kroemer, G., 2013. The hallmarks of ageing. Cell 153, 1194–1217.

Lynch, M., 2010. Evolution of the mutation rate. Trends in Genetics 26, 345–352.

Martincorena, I., Roshan, A., Gerstung, M., Ellis, P., Van Loo, P., McLaren, S., Wedge, D.C., Fullam, A., Alexandrov, L.B., Tubio, J.M., et al., 2015. Tumor evolution. High burden and pervasive positive selection of somatic mutations in normal human skin. Science 348, 880–886.

Marusyk, A., Casas-Selves, M., Henry, C.J., Zaberezhnyy, V., Klawitter, J., Christians, U., Degregori, J., 2009. Irradiation alters selection for oncogenic mutations in hematopoietic progenitors. Cancer Research 69, 7262–7269.

Marusyk, A., Porter, C.C., Zaberezhnyy, V., DeGregori, J., 2010. Irradiation selects for p53-deficient hematopoietic progenitors. PLoS Biology 8, e1000324.

McKerrell, T., Park, N., Moreno, T., Grove, C.S., Ponstingl, H., Stephens, J., Crawley, C., Craig, J., Scott, M.A., Hodkinson, C., et al., 2015. Leukemia-associated somatic mutations drive distinct patterns of age-related clonal hemopoiesis. Cell Reports 10, 1239–1245.

Mizushima, N., 2007. Autophagy: process and function. Genes and Devlopment 21, 2861–2873.

Morselli, E., Maiuri, M.C., Markaki, M., Megalou, E., Pasparaki, A., Palikaras, K., Criollo, A., Galluzzi, L., Malik, S.A., Vitale, I., et al., 2010. Caloric restriction and resveratrol promote longevity through the Sirtuin-1-dependent induction of autophagy. Cell Death and Disease 1, e10.

Nair, U., Klionsky, D.J., 2011. Activation of autophagy is required for muscle homeostasis during physical exercise. Autophagy 7, 1405–1406.

Nordling, C.O., 1953. A new theory on the cancer-inducing mechanism. British Journal of Cancer 7, 68–72.

Nowell, P.C., 1976. The clonal evolution of tumor cell populations. Science 194, 23–28.

Orr, H.A., 2009. Fitness and its role in evolutionary genetics. Nature Reviews Genetics 10, 531–539.

Pompei, F., Polkanov, M., Wilson, R., 2001. Age distribution of cancer in mice: the incidence turnover at old age. Toxicology and Industrial Health 17, 7–16.

Rangarajan, A., Hong, S.J., Gifford, A., Weinberg, R.A., 2004. Species- and cell type-specific requirements for cellular transformation. Cancer Cell 6, 171–183.

Rivlin, N., Brosh, R., Oren, M., Rotter, V., 2011. Mutations in the p53 tumor suppressor gene: important milestones at the various steps of tumorigenesis. Genes and Cancer 2, 466–474.

Roos, W.P., Kaina, B., 2013. DNA damage-induced cell death: from specific DNA lesions to the DNA damage response and apoptosis. Cancer Letters 332, 237–248.

Rosenfeldt, M.T., Ryan, K.M., 2009. The role of autophagy in tumour development and cancer therapy. Expert Reviews in Molecular Medicine 11, e36.

Rossi, D.J., Bryder, D., Zahn, J.M., Ahlenius, H., Sonu, R., Wagers, A.J., Weissman, I.L., 2005. Cell intrinsic alterations underlie hematopoietic stem cell aging. Proceedings of the National Academy of Sciences of the United States of America 102, 9194–9199.

Rostom, A., Dube, C., Lewin, G., 2007. In: Use of Aspirin and NSAIDs to Prevent Colorectal Cancer, Rockville, MD.

Rozhok, A.I., DeGregori, J., 2015. Toward an evolutionary model of cancer: considering the mechanisms that govern the fate of somatic mutations. Proceedings of the National Academy of Sciences of the United States of America 112, 8914–8921.

Rozhok, A.I., Salstrom, J.L., DeGregori, J., 2014. Stochastic modeling indicates that aging and somatic evolution in the hematopoietic system are driven by non-cell-autonomous processes. Aging 6, e1–16.

Rubin, H., 2001. The role of selection in progressive neoplastic transformation. Advances in Cancer Research 83, 159–207.

Seluanov, A., Chen, Z., Hine, C., Sasahara, T.H., Ribeiro, A.A., Catania, K.C., Presgraves, D.C., Gorbunova, V., 2007. Telomerase activity coevolves with body mass not lifespan. Aging Cell 6, 45–52.

Sidorov, I., Kimura, M., Yashin, A., Aviv, A., 2009. Leukocyte telomere dynamics and human hematopoietic stem cell kinetics during somatic growth. Experimental Hematology 37, 514–524.

Silander, O.K., Tenaillon, O., Chao, L., 2007. Understanding the evolutionary fate of finite populations: the dynamics of mutational effects. PLoS Biology 5, e94.

Smith, J.M., 1976. What determines the rate of evolution? The American Naturalist 110, 331–338.

Smith, G.S., Walford, R.L., Mickey, M.R., 1973. Lifespan and incidence of cancer and other diseases in selected long-lived inbred mice and their F1 hybrids. Journal of the National Cancer Institute 50 (5), 1195–1213.

Snippert, H.J., van der Flier, L.G., Sato, T., van Es, J.H., van den Born, M., Kroon-Veenboer, C., Barker, N., Klein, A.M., van Rheenen, J., Simons, B.D., Clevers, H., 2010. Intestinal crypt homeostasis results from neutral competition between symmetrically dividing Lgr5 stem cells. Cell 143, 134–144.

Spike, B.T., Wahl, G.M., 2011. p53, stem cells, and reprogramming: tumor suppression beyond guarding the genome. Genes and Cancer 2, 404–419.

Tian, X., Azpurua, J., Hine, C., Vaidya, A., Myakishev-Rempel, M., Ablaeva, J., Mao, Z., Nevo, E., Gorbunova, V., Seluanov, A., 2013. High-molecular-mass hyaluronan mediates the cancer resistance of the naked mole rat. Nature 499, 346–349.

Vas, V., Senger, K., Dorr, K., Niebel, A., Geiger, H., 2012a. Aging of the microenvironment influences clonality in hematopoiesis. PLoS One 7, e42080.

Vas, V., Wandhoff, C., Dorr, K., Niebel, A., Geiger, H., 2012b. Contribution of an aged microenvironment to aging-associated myeloproliferative disease. PLoS One 7, e31523.

Vascellari, M., Baioni, E., Ru, G., Carminato, A., Mutinelli, F., 2009. Animal tumour registry of two provinces in northern Italy: incidence of spontaneous tumours in dogs and cats. BMC Veterinary Research 5, 39.

Vermeulen, L., Morrissey, E., van der Heijden, M., Nicholson, A.M., Sottoriva, A., Buczacki, S., Kemp, R., Tavare, S., Winton, D.J., 2013. Defining stem cell dynamics in models of intestinal tumor initiation. Science 342, 995–998.

Vesely, M.D., Kershaw, M.H., Schreiber, R.D., Smyth, M.J., 2011. Natural innate and adaptive immunity to cancer. Annual Review of Immunology 29, 235–271.

Vijg, J., Busuttil, R.A., Bahar, R., Dolle, M.E., 2005. Aging and genome maintenance. Annals of the New York Academy of Sciences 1055, 35–47.

Vogelstein, B., Papadopoulos, N., Velculescu, V.E., Zhou, S., Diaz Jr., L.A., Kinzler, K.W., 2013. Cancer genome landscapes. Science 339, 1546–1558.

Wang, J.C., Doedens, M., Dick, J.E., 1997. Primitive human hematopoietic cells are enriched in cord blood compared with adult bone marrow or mobilized peripheral blood as measured by the quantitative in vivo SCID-repopulating cell assay. Blood 89, 3919–3924.

Welch, J.S., Ley, T.J., Link, D.C., Miller, C.A., Larson, D.E., Koboldt, D.C., Wartman, L.D., Lamprecht, T.L., Liu, F., Xia, J., et al., 2012. The origin and evolution of mutations in acute myeloid leukemia. Cell 150, 264–278.

Westphalen, C.B., Asfaha, S., Hayakawa, Y., Takemoto, Y., Lukin, D.J., Nuber, A.H., Brandtner, A., Setlik, W., Remotti, H., Muley, A., et al., 2014. Long-lived intestinal tuft cells serve as colon cancer-initiating cells. Journal of Clinical Investigation 124, 1283–1295.

Wright, D.E., Wagers, A.J., Gulati, A.P., Johnson, F.L., Weissman, I.L., 2001. Physiological migration of hematopoietic stem and progenitor cells. Science 294, 1933–1936.

Xie, M., Lu, C., Wang, J., McLellan, M.D., Johnson, K.J., Wendl, M.C., McMichael, J.F., Schmidt, H.K., Yellapantula, V., Miller, C.A., et al., 2014. Age-related mutations associated with clonal hematopoietic expansion and malignancies. Nature Medicine 20, 1472–1478.

Yuan, R., Tsaih, S.W., Petkova, S.B., Marin de Evsikova, C., Xing, S., Marion, M.A., Bogue, M.A., Mills, K.D., Peters, L.L., Bult, C.J., et al., 2009. Aging in inbred strains of mice: study design and interim report on median lifespans and circulating IGF1 levels. Aging Cell 8, 277–287.

Chapter 13

Evolution of the Human Leukocyte Antigen System

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INTRODUCTION

The human leukocyte antigen (HLA) genes are located on the short arm of chromosome six within the major histocompatibility complex (MHC) that includes other genes with immune-related functions. The HLA genes are distinguished by their exceptional polymorphism with over 10,000 alleles described to date (Robinson et al., 2015), which is driven by the long-standing evolutionary arms race with pathogens (Prugnolle et al., 2005). This coevolution between host and pathogens has occurred as the HLA molecules play a central role in adaptive immunity by presenting to T cells fragments of self and nonself (ie, microbial) proteins. The importance of this interplay in the context of infectious disease is evidenced by the various mechanisms utilized by pathogens to evade HLA-restricted T cell immune responses (Nolan et al., 2006).

The relevance of the HLA genes in the context of disease is further emphasized by the large volume of disease association studies, both case-control studies and genome-wide association studies (GWAS), that have repeatedly identified the HLA genes, or the MHC, as a hot spot for candidate disease gene(s). For a number of autoimmune and infectious diseases HLA remains the strongest genetic predictor of outcome. However, although the HLA genes have been identified in many disease association studies, the actual causal mechanism for many of these diseases has only recently been elucidated for some, but for others, remains elusive. The main obstacle to better understanding the specific involvement of the HLA genes in disease is due to their inherent characteristics: multicopy gene family with overlapping functions, extreme allelic polymorphism, and extensive linkage disequilibrium (LD) between different loci.

Multicopy Gene Families Due to Segmental Duplications: Evolution of Different but Related Functions

The HLA genes can be broadly grouped into two types based on functional and structural features: class I and class II. Phylogenetic analysis of the different HLA class I and II genes suggest they are likely to have diverged about 500 million years ago (mya) from a common ancestor, with the different HLA class II loci diverging from each other about 170−200 mya (Nei et al., 1997). The different HLA class I loci are thought to have diverged later than the duplication of the class II genes but a HLA class I-like molecule is likely to have been part of the "proto-MHC" given the existence of MHC class I-like molecules, and not class II-like genes, on other chromosomes suggesting the existence of an ancestor prior to large-scale genome duplications in vertebrate evolution (reviewed in Parham, 2015).

The HLA class I locus HLA-F was present in the primate genome at least 46−66 mya giving rise to HLA-G and E, and then HLA-A and B about 35−49 mya (Piontkivska and Nei, 2003). The duplication of HLA-B giving rise to HLA-C is thought to have occurred about 21−28 mya. The phylogenetic clustering of the HLA and homologous primate HLA sequences supports these divergence times. For example, orthologs of HLA-E are present in Old and New World Monkeys, while HLA-A and HLA-B are shared with other apes and Old World Monkeys, and HLA-C is shared only with chimpanzee, gorilla, and orangutan (Adams and Parham, 2001). Interestingly, in contrast to humans, many of the nonhuman primates have additional HLA-A and -B−like genes that are likely to be lineage specific and may have evolved nonoverlapping functions (Adams and Parham, 2001).

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00013-2

Early genetic studies by Nei et al. showed an interrelationship between species for the different HLA genes rather than close relationships for the different genes within each species (ie, the individual loci form single clusters; as also shown in Fig. 13.1 based on currently available HLA sequences at www.imgt.org) (Nei et al., 1997). This relationship suggested limited evidence for interlocus gene conversion or recombination and that the genes are likely to reflect a mode of birth and death evolution. In this model, new genes are created by duplications of genes with some of these new genes deleted from the region or becoming nonfunctional by deleterious mutations; surviving copies can evolve with the development of distinct functions (Nei et al., 1997) as is clearly observed for the HLA genes.

The HLA class II genes encode glycoproteins that exist as a heterodimer of an α and β chain encoded by different, but closely linked, genes in the MHC. These molecules are predominantly expressed on professional antigen-presenting cells and are involved in presenting extracellular antigens to helper T cells. The loci include the

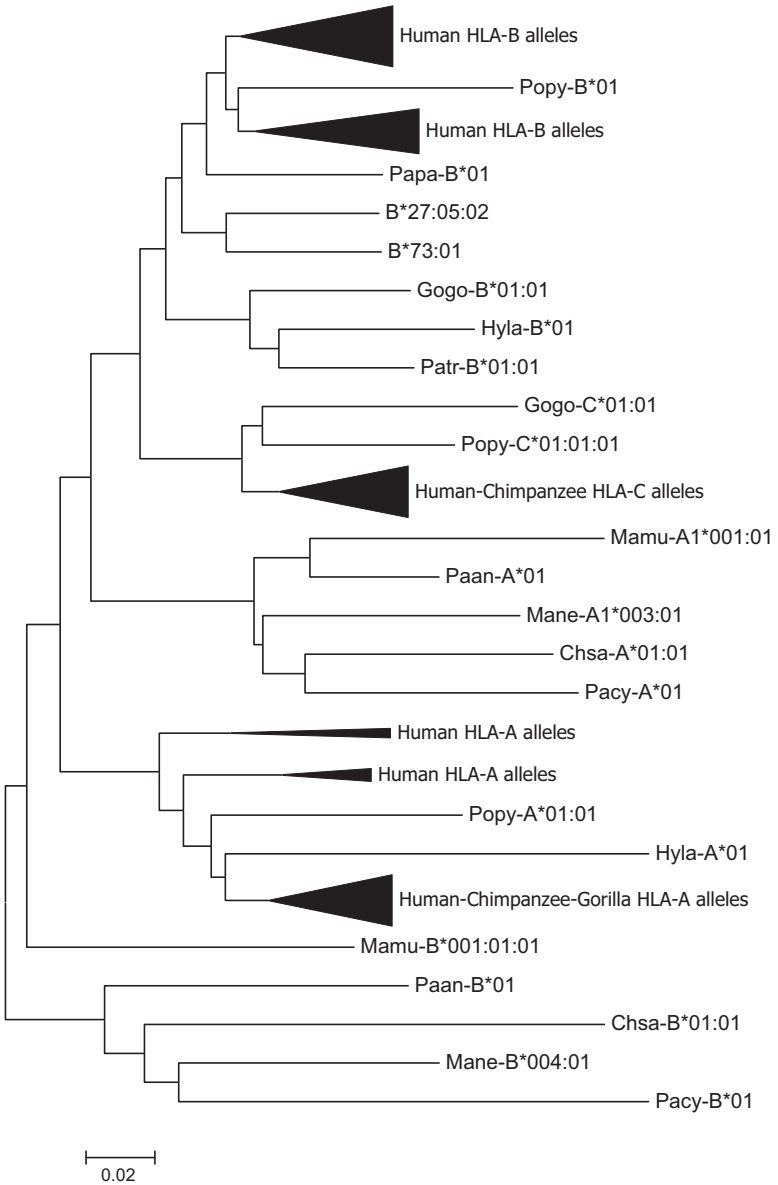

FIGURE 13.1 Phylogenetic analysis of primate major histocompatibility complex (MHC) class I exon 2 and 3 sequences using the neighbor-joining method. MHC sequences obtained from www.imgt.org. Apes include *Patr*, Common Chimpanzee; *Gogo*, Western Gorilla; *Popy*, Bornean Orangutan; *Papa*, Bonobo; *Hyla*, Lar Gibbon. Old World Monkeys include *Pacy*, Yellow Baboon; *Mamu*, Rhesus Monkey; *Mane*, Southern Pig-Tailed Macaque; *Paan*, Olive Baboon; *Chsa*, Green Monkey. Human HLA class I sequences include all alleles to two-digit resolution. *Distance bar* indicates substitutions/site.

highly diverse HLA-DR, -DQ genes, and the less diverse HLA-DM, -DP genes. In contrast, the HLA class I genes encode glycoproteins that comprise three extracellular domains, including the α1 and α2 domains that form the peptide binding region, and a conserved α3 domain that is noncovalently bound to β2-microglobulin, which is encoded on a different chromosome.

The HLA class I genes can be further separated into the highly polymorphic classical class Ia genes HLA-A, -B, and -C that are expressed on all nucleated cells and the nonclassical HLA class Ib genes HLA-E, -G, and -F that are relatively oligomorphic and are typically restricted in expression to specific tissues or cell types. There are also a number of HLA class I pseudogenes (eg, HLA-J). The classical class Ia proteins are associated with presenting self and nonself peptides to cytotoxic T cells and the majority of variation between alleles is concentrated in the peptide-binding domains. These glycoproteins also act as ligands for the Natural Killer (NK) cell killer immunoglobulin-like receptors (KIRs) but their propensity to act as KIR ligands varies (Wilson et al., 2000; Trowsdale, 2001) with only a subset of HLA-A and -B alleles able to bind NK receptors with HLA-C alleles likely to be the dominant NK cell receptor ligand. This dual functionality of the HLA class I genes represents two coevolving strategies and reflects the development of nonoverlapping functions since the duplication of ancestral HLA class I genes.

The functional specialization of the closely related HLA class I genes following duplication is also supported by a study examining HLA class I binding preferences for peptides derived from human proteins and different virus families (Hertz et al., 2011). The analysis in this study showed that binding preferences for HLA-A alleles and for those HLA-B lineages that predate the human-chimpanzee split favor conserved epitopes in human proteins and DNA viruses such as *Herpesviridae* and *Adenoviridae* in which host mimicry is a prominent mechanism of immune evasion. The longer coevolution with these viruses suggest that this pattern of targeting would fit with such viruses exploiting "holes" in the mature T cell repertoire created by thymic negative selection of self-reactive T cells (Louzoun et al., 2006; Vider-Shalit et al., 2007; Frankild et al., 2008), whereas HLA-B alleles, in general, efficiently target conserved epitopes in RNA viruses (including the human-specific *Paramyxoviridae*) whose replicative characteristics allow them to additionally evade HLA-restricted immunity by mutational escape. The same analysis was then used on a well-characterized cohort of HIV-1-infected individuals to show that HLA-B binding efficiency (based on a subject's HLA genotype) to conserved T cell epitopes strongly correlated with viral load, supporting the known immunological data showing HLA-B responses are important in determining the natural history of HIV infection (Kiepiela et al., 2007). This study and others suggest different evolutionary pressures on the HLA class I loci (Prugnolle et al., 2005; Watkins et al., 1992) and may reflect different rates of change including via intra-allelic recombination (Piontkivska and Nei, 2003).

The functional repertoire of the nonclassical class I proteins has not been as well characterized. HLA-E displays the least polymorphism among the HLA class I loci, having, in Caucasian populations, only two alleles that differ by a single amino acid (Ulbrecht et al., 1999). The discovery that HLA-E binds conserved strictly nonameric leader peptides of coexpressed HLA-A, -B, -C, and -G and ligates with inhibitory CD94/NKG2A NK receptors suggested that this locus evolved to monitor HLA class I expression, the downregulation of which is an important immune evasion mechanism of many pathogens (Borrego et al., 1998). Cytomegalovirus (CMV) has devised an interesting counter measure for the immune-surveillance function of HLA-E by actively upregulating the expression of HLA-E (while downregulating expression of classical HLA class I) (Tomasec et al., 2000; Wang et al., 2002) and loading viral peptides identical to HLA leader sequences onto HLA-E through a TAP-independent mechanism, leading to inhibition of NK-mediated lysis of CMV-infected cells (Wang et al., 2002). HLA-G is also linked to the immunomodulation of NK cell function, particularly in the context of the fetal−maternal interface, as it can act as a ligand for another type of inhibitory NK cell receptor (*KIR2DL4*) (reviewed in Amodio et al., 2014).

Recent data suggest a novel HLA-E-restriction element for T cells via the presentation of noncanonical peptides derived from stress-related and pathogen-associated proteins (reviewed in Pietra et al., 2009). For example, studies have demonstrated HLA-E-restricted antigen-specific $CD8^+$ T cell responses activated through αβ T cell receptors in a number of infections, including those caused by Epstein-Barr virus (EBV), *Mycobacterium tuberculosis*, *Salmonella*, Hepatitis C virus (HCV), and against HLA-E-expressing tumors (Pietra et al., 2010). Furthermore, HLA-E-restricted regulatory $CD8^+$ T cells suppressed activation of simian immunodeficiency virus (SIV)-infected $CD4^+$ T cells inhibiting viral transmission in the macaque SIV vaccine model (Andrieu et al., 2014). These observations suggest the involvement in NK and T cell function is a feature of classical and nonclassical HLA class I genes but the mode of action and likely extent of involvement in the innate and adaptive arm of the immune response varies.

A detailed examination of the duplication process for the HLA class I genes reveals that the HLA class I genes and the closely linked polymorphic MHC class I chain related (MIC) genes form part of segments that have duplicated over time, likely facilitated by retroelements including human endogenous retroviruses (Gaudieri et al., 1999a; Kulski et al., 1999). This process of segmental duplication in the MHC class I region has resulted in the

generation of sets of closely related HLA and MIC gene families and in some cases leading to haplotypes that have specific combinations of alleles for these multicopy gene families (discussed later in this chapter). However, in some instances the segmental duplications may be imperfect or are associated with large deletions creating nonfunctional gene products. For example, the HLA-B*48 haplotype in East Asian populations contains a large 100 kb deletion in the region between MICB and HLA-B resulting in a null MICA allele and a premature stop in MICB (Komatsu-Wakui et al., 2001). Similarly, in the chimpanzee, the same region has a large deletion of ~95 kb creating a single fused MICA/MICB gene (Anzai et al., 2003). Other large insertions/deletions occur in humans and other primates in the area containing and surrounding HLA-A to HLA-F (Watanabe et al., 1997) that also contains a number of HLA class I pseudogenes and gene fragments suggesting recent expansion/contraction in the region with unknown functional consequences.

Extensive Allelic Polymorphism: Evidence for Multiple Selection Pressures

Studies on the genetic variation between human HLA alleles suggested the maintenance of the observed diversity in the population was due to overdominant or heterozygote advantage based on the higher rate of nonsynonymous (replacement) changes over synonymous (silent) changes in the peptide binding region compared to the nonpeptide binding regions of the protein (Hughes and Nei, 1988) and the presence of alleles that predate speciation events (trans-species polymorphism) (reviewed in Hughes and Yeager, 1998). Such heterozygote advantage would suggest that individuals expressing different HLA alleles at the different loci would be at an advantage in an environment in which they are exposed to a wide array of pathogens, as originally proposed by Doherty and Zinkernagel (1975) for the murine H-2 system that is homologous to the HLA system. In essence, each HLA allele "sees" a unique set of processed pathogen peptides (epitopes) and accordingly individuals who express different HLA types (heterozygotes) are in principle able to present a broader response and provide better protection. Certainly this has been shown in the context of HLA class I for the highly mutable pathogens HIV (Carrington et al., 1999) and HCV (Hraber et al., 2007). A systematic analysis of the DNA sequences of thousands of alleles from about 200 populations supports a refinement of this model called "asymmetric overdominant" selection suggesting an advantage for those individuals expressing distant HLA molecules (Buhler and Sanchez-Mazas, 2011). Furthermore, given the adaptive potential of many pathogens, rare HLA alleles in the population may be favored resulting in frequency-dependent selection, but this mode of evolution alone is unlikely to explain the long-term maintenance of the polymorphism exhibited at the HLA loci. Evidence of gene conversion also exists to support the extreme variation observed in this genetic system, particularly for HLA-B (Buhler and Sanchez-Mazas, 2011).

The HLA genetic system may also be subject to sexual selection. In the American Hutterites, an example of an isolated founder population, mate choice was found to be favored between couples with dissimilar HLA types and in turn these couples were more fertile than HLA concordant couples (Ober, 1999). The influence of HLA on mate choice has been an intriguing area given the use of HLA (or equivalent in other species) peptides as chemosensory signals (Leinders-Zufall et al., 2004; Milinski et al., 2013), the preference for MHC-dissimilarity based on odor in some populations (Chaix et al., 2008 and human studies reviewed in Havlicek and Roberts, 2009), and the close proximity of the olfactory receptor genes to the HLA genes in the MHC (Ziegler et al., 2010).

There are also data to support an intriguing mode of adaptation via introgression of DNA from archaic hominids. Parham et al. have suggested that a substantial proportion of the HLA alleles currently observed in Eurasians is from admixture with Neandertals and the Denisovans, a sister group to Neandertals, that lived in Eurasia about 30,000−200,000 years ago (Abi-Rached et al., 2011). The suggestion stems from the observation of the HLA-C variants (HLA-C*12 and C*15) found in the Denisovan genome that are linked to the HLA-B allele HLA-B*73, an allele that appears in West Asian populations but absent from African tribes although similar to alleles in chimpanzees and gorillas. In addition, HLA-A*11 with HLA-C*12 and C*15 haplotypes may also have been obtained via admixture. Similar analyses suggest that Neandertals contributed HLA-B*07, B*51, C*07:02, and C*16:02. It is likely that selection and drift had a major influence on the early hominid populations given the relatively small effective population sizes and it would have been advantageous for a population to obtain such preexisting allele(s) in a new environment with a different pathogen load. For example, HLA-A*11 provides T cell-mediated protection against some strains of EBV (de Campos-Lima et al., 1993), and when binding an EBV peptide can bind *KIR3DL2* (only one of two ligands for this KIR) (Hansasuta et al., 2004).

It is not only the peptide binding domains of the HLA genes within the MHC that are characterized by high levels of diversity but also in non-HLA genes and intervening sequences—some of which is likely explained by "hitchhiking" effects (Gaudieri et al., 1999b, 2000). In fact there is a strong inverse correlation between diversity in the intergenic regions of the MHC and sites of recombination (Gaudieri et al., 2000). These regions in turn refine regions of disease susceptibility that can limit GWAS and

other genetic association studies. Another outcome from this phenomenon is the formation of polymorphic frozen blocks that contain a certain combination of alleles at different genes, many of which have an immunological function such as HLA and MIC (Dawkins et al., 1999).

Potential Bottlenecks

The extent to which constrictions in HLA repertoires may have been caused by the negative selection effect of past pathogens is difficult to determine. It is known that European contact with native Amerindians led to transmissions of measles and small pox, among other pathogens, with devastating consequences on population sizes (McMichael, 2004). The case for pathogen-associated bottlenecks is much more clear for our nearest closest living relatives, the chimpanzee, with whom humans shared a common ancestor about 5 mya (McAdam et al., 1995). Though this would predict a large degree of sharing of HLA-A and -B lineages, there is a marked specific restriction in MHC class I intron variation and numbers of unique alleles in chimps compared to humans, due to a probable "selective sweep" about 2 mya, predating the subspeciation of chimpanzees (Abi-Rached et al., 2011). This is likely to have been caused by an ancient primate lentivirus resembling SIVcpz/HIV-1, which killed a large number of individuals and selected out a restricted range of Patr class I allotypes. Thus modern chimps, particularly those in West African populations, appear adapted to SIV as a nonpathogenic infection. This would account for data showing similar peptide binding characteristics of Patr class I allotypes and HLA-B alleles HLA-B*57:01 and -B*27:05 associated with preferential restriction of conserved epitopes in HIV and natural antiviral control (de Groot et al., 2010; Gleimer et al., 2011; van Deutekom et al., 2011).

Extensive Linkage Disequilibrium Between Human Leukocyte Antigen Loci

The MHC is characterized by extensive LD that can cover up to 4 Mb of sequence. From the original complotypes to ancestral haplotypes it has been known that there are combinations of alleles that are inherited *en bloc* (Dawkins et al., 1999). The reasoning behind the maintenance of such combinations—for example MICA/B alleles and HLA-B/C combinations is still unclear—but some studies of cell lines with different ancestral haplotypes have shown varying levels of immune responsiveness (eg, levels of tumour necrosis factor) (Abraham et al., 1993). The combination of specific HLA class I and class II alleles in MHC haplotypes that appear to be well maintained in populations is intriguing and may reflect some adaptive advantage as suggested by Penman et al. (2013) who provide theoretical evidence that pathogen selection can drive long-range and long-term haplotypes.

An interesting new model for the MHC has been proposed, termed the "associative balancing complex evolution," which attempts to explain the many features of the MHC such as extensive diversity at both HLA and non-HLA genes, epistasis of the multicopy gene families resulting in the haplotype structure and the strong association of the MHC with different diseases (van Oosterhout, 2009). One of the main components of the model suggests that potential recessive disease-causing mutations are maintained in the region due to a likely lack of purifying selection resulting in a "sheltered load". Disease manifests only when homozygosity results, which is likely to be relatively rare due to the allelic nature of the MHC and selection against this form, also leading to maintenance of epistasis of the genes within the haplotype blocks resulting in the described polymorphic frozen blocks that span the MHC (Dawkins et al., 1999).

COMPETING EVOLUTIONARY PRESSURES: HLA–NK CELL INTERACTION

As mentioned previously, aside from presenting peptides to T cells, HLA class I proteins also act as ligands for NK cell receptors. NK cells constitute a crucial component of the host's innate immune response, but data also show that NK cells may modulate the host's adaptive immune response by directly deleting activated $CD4^+$ and $CD8^+$ T cells (Nielsen et al., 2012; Peppa et al., 2013), hence these cells are important contributors to the overall host immune response to pathogens and disease. The cytotoxic capacity of NK cells is regulated via signals derived from a complex array of inhibitory and activating receptors such as the variable KIRs and the more conserved NKG2 family including CD94/NKG2A that binds HLA-E (Jamil and Khakoo, 2011). These receptors allow NK cells to sample cells for the presence of HLA class I molecules that are expressed on healthy cells (indicate "normal self" to the immune system); however, target cells, such as virally infected cells or tumor cells, typically have low or no expression of HLA class I molecules on their surface in order to escape detection from cytotoxic $CD8^+$ T cells, and they can be recognized and lysed by NK cells in a process referred to as missing-self recognition (Karre et al., 1986).

The genes that encode the KIR proteins are present in the leukocyte receptor complex on chromosome 19 and the genomic region shares some features with the MHC; extensive LD between closely related KIR members, genetic diversity (although unlikely to be as diverse as the HLA genes even with greater sampling of KIR genes), and evidence for balancing selection. Furthermore, there are known KIR haplotypes (mainly of type A or B) and they

can differ in gene content (A has mainly inhibitory KIRs and also found in chimpanzees while B is only found in humans) and frequency in different populations (Parham and Moffett, 2013). Accordingly, the HLA/KIR interaction is highly variable and this evolution, as for the HLA/T cell interaction, is driven by selective pressure from exposure to pathogens (Parham et al., 2010; Hershberger et al., 2001; Khakoo et al., 2000). Supporting evidence for this selection pressure includes reports showing the presence of particular combinations of HLA class I alleles and KIRs within a host that have been associated with a number of infectious disease outcomes (Martin et al., 2002; Khakoo et al., 2004). However, the HLA/KIR interaction is also important in reproduction (incurring significant fitness costs based on certain HLA/KIR combinations) as reviewed by Moffett and Colucci (2015) and the frequency of the KIR haplotypes and HLA ligands in different human populations likely reflects this evolutionary interplay. Interestingly, although human and chimpanzee have closely related homologs for HLA-A, -B, and -C the KIR gene content and haplotypes are different, reflecting lineage-specific evolution.

Finally, data suggest that the sequence content of the peptide presented by the HLA class I molecule may be relevant in the context of NK cells (Alter et al., 2011) and for specific HLA/KIR interactions (Holzemer et al., 2015), akin to the viral immune escape mutations known to affect the T cell−HLA peptide complex and observed at the population level as HLA-associated viral escape (Moore et al., 2002). Furthermore, the binding area of the HLA/KIR interaction overlaps with that of the HLA/T cell receptor (Boyington et al., 2000). Collectively, these data suggest the two interactions are not independent and reflect a competing evolutionary pressure on the HLA system to maintain its role in NK cell function but retain the ability to present varying sets of peptides to T cells.

FUTURE CONSIDERATIONS

Influence of Human Leukocyte Antigen on the Microbiome (Commensal and Symbiotic Microorganisms)

Although much has been examined in the context of HLA (and the MHC) and infectious diseases, there have been few studies examining the influence of HLA on the human microbiome and how this interaction may have influenced the evolution of the HLA system or vice versa. For example, it is known that the human diet influences the gut microbiome, and levels of protein and carbohydrates have been shown to influence the bacterial enterotype in the gut (Arumugam et al., 2011). Dietary adaptations throughout human evolution have been documented and potentially may have affected this host immune/gut microbiome interaction.

The human microbiota is associated with an increasing number of phenotypes and is influenced by early life interactions as well as later environmental insults. The gut contains the most diverse and largest community of commensal and symbiotic microorganisms in the body. Genetics (evidenced by transgenerational inheritance of microbiomes) and environment factors influence the composition of this community and not surprisingly, diet is an important factor as well as infections. It is likely that the microbiome is important in shaping the host's adaptive immune response, including tolerance to self-antigens. There have been some studies that have examined how HLA may influence the microbiota. Rishi et al. have reviewed data from human and animal studies to better understand the immunogenetics of the gut microbiota (Marietta et al., 2015). A comparison of monozygotic (MZ) versus dizygotic (DZ) twins showed a higher concordance rate of pathogen carriage in MZ over DZ twins, as may be expected given heritability for a phenotype (in this case pathogen load) (reviewed in Marietta et al., 2015). Another example using a humanized mouse model showed animals with the HLA-DRB1*04 alleles, associated with differential predisposition to rheumatoid arthritis, exhibited varied gut microbiomes suggesting these molecules may be involved in shaping the microorganisms that colonize the gut (Taneja, 2014; Gomez et al., 2012); similar results were shown for humans (Scher et al., 2013). Another animal model showed the presence of HLA-B27, associated with ankylosing spondylitis, altered the gut microbiome (Lin et al., 2014). The HLA-DQ2 allele associated with the development to celiac disease was found to influence microbial diversity in infants (Olivares et al., 2015; De Palma et al., 2010). It remains to be seen how critical the HLA repertoire we inherit and our environment influences our microbiome—not only in the gut but elsewhere in the body.

CONCLUSIONS

The ability to differentiate self and nonself with immunological memory is common to vertebrates. In humans and many other species the HLA or homologous genes maintain this function. In humans, the HLA genes reside within the MHC; an area of the genome that is a reservoir for immune-related genes involved in NK cell activation, inflammation, and antigen processing supporting the large volume of studies that have shown an association between the MHC and disease. However, the features of the MHC have also provided geneticists with an information-rich template from which to examine our ancestry, migrations, diet, and interactions with pathogens. While many specific drivers of MHC evolution have been elucidated, there is still much

more to be understood, particularly in the less studied nonclassical HLA loci, the HLA receptors such as KIRs, and in variable HLA expression (as an additional layer of polymorphism) that has biological consequences as indicated for HIV infection (Apps et al., 2013). It is hoped that continued investment in understanding this aspect of human variation will continue to provide benefits to human health and the ongoing human story.

REFERENCES

Abi-Rached, L., Jobin, M.J., Kulkarni, S., McWhinnie, A., Dalva, K., Gragert, L., et al., 2011. The shaping of modern human immune systems by multiregional admixture with archaic humans. Science 334 (6052), 89–94.

Abraham, L.J., French, M.A., Dawkins, R.L., 1993. Polymorphic MHC ancestral haplotypes affect the activity of tumour necrosis factor-alpha. Clinical and Experimental Immunology 92 (1), 14–18.

Adams, E.J., Parham, P., 2001. Species-specific evolution of MHC class I genes in the higher primates. Immunological Reviews 183, 41–64.

Alter, G., Heckerman, D., Schneidewind, A., Fadda, L., Kadie, C.M., Carlson, J.M., et al., 2011. HIV-1 adaptation to NK-cell-mediated immune pressure. Nature 476 (7358), 96–100.

Amodio, G., Sales de Albuquerque, R., Gregori, S., 2014. New insights into HLA-G mediated tolerance. Tissue Antigens 84 (3), 255–263.

Andrieu, J.M., Chen, S., Lai, C., Guo, W., Lu, W., 2014. Mucosal SIV vaccines comprising inactivated virus particles and bacterial adjuvants induce CD8(+) T-regulatory cells that suppress SIV-positive CD4(+) T-cell activation and prevent SIV infection in the macaque model. Frontiers in Immunology 5, 297.

Anzai, T., Shiina, T., Kimura, N., Yanagiya, K., Kohara, S., Shigenari, A., et al., 2003. Comparative sequencing of human and chimpanzee MHC class I regions unveils insertions/deletions as the major path to genomic divergence. Proceedings of the National Academy of Sciences of the United States of America 100 (13), 7708–7713.

Apps, R., Qi, Y., Carlson, J.M., Chen, H., Gao, X., Thomas, R., et al., 2013. Influence of HLA-C expression level on HIV control. Science 340 (6128), 87–91.

Arumugam, M., Raes, J., Pelletier, E., Le Paslier, D., Yamada, T., Mende, D.R., et al., 2011. Enterotypes of the human gut microbiome. Nature 473 (7346), 174–180.

Borrego, F., Ulbrecht, M., Weiss, E.H., Coligan, J.E., Brooks, A.G., 1998. Recognition of human histocompatibility leukocyte antigen (HLA)-E complexed with HLA class I signal sequence-derived peptides by CD94/NKG2 confers protection from natural killer cell-mediated lysis. The Journal of Experimental Medicine 187 (5), 813–818.

Boyington, J.C., Motyka, S.A., Schuck, P., Brooks, A.G., Sun, P.D., 2000. Crystal structure of an NK cell immunoglobulin-like receptor in complex with its class I MHC ligand. Nature 405 (6786), 537–543.

Buhler, S., Sanchez-Mazas, A., 2011. HLA DNA sequence variation among human populations: molecular signatures of demographic and selective events. PloS One 6 (2), e14643.

de Campos-Lima, P.O., Gavioli, R., Zhang, Q.J., Wallace, L.E., Dolcetti, R., Rowe, M., et al., 1993. HLA-A11 epitope loss isolates of Epstein–Barr virus from a highly A11+ population. Science 260 (5104), 98–100.

Carrington, M., Nelson, G.W., Martin, M.P., Kissner, T., Vlahov, D., Goedert, J.J., et al., 1999. HLA and HIV-1: heterozygote advantage and B*35-Cw*04 disadvantage. Science 283 (5408), 1748–1752.

Chaix, R., Cao, C., Donnelly, P., 2008. Is mate choice in humans MHC-dependent? PLoS Genetics 4 (9), e1000184.

Dawkins, R., Leelayuwat, C., Gaudieri, S., Tay, G., Hui, J., Cattley, S., et al., 1999. Genomics of the major histocompatibility complex: haplotypes, duplication, retroviruses and disease. Immunological Reviews 167, 275–304.

De Palma, G., Capilla, A., Nadal, I., Nova, E., Pozo, T., Varea, V., et al., 2010. Interplay between human leukocyte antigen genes and the microbial colonization process of the newborn intestine. Current Issues in Molecular Biology 12 (1), 1–10.

van Deutekom, H.W., Hoof, I., Bontrop, R.E., Kesmir, C., 2011. A comparative analysis of viral peptides presented by contemporary human and chimpanzee MHC class I molecules. Journal of Immunology 187 (11), 5995–6001.

Doherty, P.C., Zinkernagel, R.M., 1975. Enhanced immunological surveillance in mice heterozygous at the H-2 gene complex. Nature 256 (5512), 50–52.

Frankild, S., de Boer, R.J., Lund, O., Nielsen, M., Kesmir, C., 2008. Amino acid similarity accounts for T cell cross-reactivity and for "holes" in the T cell repertoire. PloS One 3 (3), e1831.

Gaudieri, S., Kulski, J.K., Dawkins, R.L., Gojobori, T., 1999a. Different evolutionary histories in two subgenomic regions of the major histocompatibility complex. Genome Research 9 (6), 541–549.

Gaudieri, S., Kulski, J.K., Dawkins, R.L., Gojobori, T., 1999b. Extensive nucleotide variability within a 370 kb sequence from the central region of the major histocompatibility complex. Gene 238 (1), 157–161.

Gaudieri, S., Dawkins, R.L., Habara, K., Kulski, J.K., Gojobori, T., 2000. SNP profile within the human major histocompatibility complex reveals an extreme and interrupted level of nucleotide diversity. Genome Research 10 (10), 1579–1586.

Gleimer, M., Wahl, A.R., Hickman, H.D., Abi-Rached, L., Norman, P.J., Guethlein, L.A., et al., 2011. Although divergent in residues of the peptide binding site, conserved chimpanzee Patr-AL and polymorphic human HLA-A*02 have overlapping peptide-binding repertoires. Journal of Immunology 186 (3), 1575–1588.

Gomez, A., Luckey, D., Yeoman, C.J., Marietta, E.V., Berg Miller, M.E., Murray, J.A., et al., 2012. Loss of sex and age driven differences in the gut microbiome characterize arthritis-susceptible 0401 mice but not arthritis-resistant 0402 mice. PloS One 7 (4), e36095.

de Groot, N.G., Heijmans, C.M., Zoet, Y.M., de Ru, A.H., Verreck, F.A., van Veelen, P.A., et al., 2010. AIDS-protective HLA-B*27/B*57 and chimpanzee MHC class I molecules target analogous conserved areas of HIV-1/SIVcpz. Proceedings of the National Academy of Sciences of the United States of America 107 (34), 15175–15180.

Hansasuta, P., Dong, T., Thananchai, H., Weekes, M., Willberg, C., Aldemir, H., et al., 2004. Recognition of HLA-A3 and HLA-A11 by KIR3DL2 is peptide-specific. European Journal of Immunology 34 (6), 1673–1679.

Havlicek, J., Roberts, S.C., 2009. MHC-correlated mate choice in humans: a review. Psychoneuroendocrinology 34 (4), 497–512.

Hershberger, K.L., Shyam, R., Miura, A., Letvin, N.L., 2001. Diversity of the killer cell Ig-like receptors of rhesus monkeys. Journal of Immunology 166 (7), 4380–4390.

Hertz, T., Nolan, D., James, I., John, M., Gaudieri, S., Phillips, E., et al., 2011. Mapping the landscape of host-pathogen coevolution: HLA class I binding and its relationship with evolutionary conservation in human and viral proteins. Journal of Virology 85 (3), 1310–1321.

Holzemer, A., Thobakgale, C.F., Jimenez Cruz, C.A., Garcia-Beltran, W.F., Carlson, J.M., van Teijlingen, N.H., et al., 2015. Selection of an HLA-C*03:04-restricted HIV-1 p24 Gag sequence variant is associated with viral escape from KIR2DL3+ natural killer cells: data from an observational cohort in South Africa. PLoS Medicine 12 (11), e1001900.

Hraber, P., Kuiken, C., Yusim, K., 2007. Evidence for human leukocyte antigen heterozygote advantage against hepatitis C virus infection. Hepatology 46 (6), 1713–1721.

Hughes, A.L., Nei, M., 1988. Pattern of nucleotide substitution at major histocompatibility complex class I loci reveals overdominant selection. Nature 335 (6186), 167–170.

Hughes, A.L., Yeager, M., 1998. Natural selection and the evolutionary history of major histocompatibility complex loci. Frontiers in Bioscience: A Journal and Virtual Library 3, d509–d516.

Jamil, K.M., Khakoo, S.I., 2011. KIR/HLA interactions and pathogen immunity. Journal of Biomedicine & Biotechnology 2011, 298348.

Karre, K., Ljunggren, H.G., Piontek, G., Kiessling, R., 1986. Selective rejection of H-2-deficient lymphoma variants suggests alternative immune defence strategy. Nature 319 (6055), 675–678.

Khakoo, S.I., Rajalingam, R., Shum, B.P., Weidenbach, K., Flodin, L., Muir, D.G., et al., 2000. Rapid evolution of NK cell receptor systems demonstrated by comparison of chimpanzees and humans. Immunity 12 (6), 687–698.

Khakoo, S.I., Thio, C.L., Martin, M.P., Brooks, C.R., Gao, X., Astemborski, J., et al., 2004. HLA and NK cell inhibitory receptor genes in resolving hepatitis C virus infection. Science 305 (5685), 872–874.

Kiepiela, P., Ngumbela, K., Thobakgale, C., Ramduth, D., Honeyborne, I., Moodley, E., et al., 2007. $CD8^+$ T-cell responses to different HIV proteins have discordant associations with viral load. Nature Medicine 13 (1), 46–53.

Komatsu-Wakui, M., Tokunaga, K., Ishikawa, Y., Leelayuwat, C., Kashiwase, K., Tanaka, H., et al., 2001. Wide distribution of the MICA-MICB null haplotype in East Asians. Tissue Antigens 57 (1), 1–8.

Kulski, J.K., Gaudieri, S., Martin, A., Dawkins, R.L., 1999. Coevolution of PERB11 (MIC) and HLA class I genes with HERV-16 and retroelements by extended genomic duplication. Journal of Molecular Evolution 49 (1), 84–97.

Leinders-Zufall, T., Brennan, P., Widmayer, P., Prashanth, C.S., Maul-Pavicic, A., Jager, M., et al., 2004. MHC class I peptides as chemosensory signals in the vomeronasal organ. Science 306 (5698), 1033–1037.

Lin, P., Bach, M., Asquith, M., Lee, A.Y., Akileswaran, L., Stauffer, P., et al., 2014. HLA-B27 and human β2-microglobulin affect the gut microbiota of transgenic rats. PloS One 9 (8), e105684.

Louzoun, Y., Vider, T., Weigert, M., 2006. T-cell epitope repertoire as predicted from human and viral genomes. Molecular Immunology 43 (6), 559–569.

Marietta, E., Rishi, A., Taneja, V., 2015. Immunogenetic control of the intestinal microbiota. Immunology 145 (3), 313–322.

Martin, M.P., Gao, X., Lee, J.H., Nelson, G.W., Detels, R., Goedert, J.J., et al., 2002. Epistatic interaction between KIR3DS1 and HLA-B delays the progression to AIDS. Nature Genetics 31 (4), 429–434.

McAdam, S.N., Boyson, J.E., Liu, X., Garber, T.L., Hughes, A.L., Bontrop, R.E., et al., 1995. Chimpanzee MHC class I A locus alleles are related to only one of the six families of human A locus alleles. Journal of Immunology 154 (12), 6421–6429.

McMichael, A.J., 2004. Environmental and social influences on emerging infectious diseases: past, present and future. Philosophical Transactions of the Royal Society of London Series B, Biological Sciences 359 (1447), 1049–1058.

Milinski, M., Croy, I., Hummel, T., Boehm, T., 2013. Major histocompatibility complex peptide ligands as olfactory cues in human body odour assessment. Proceedings Biological Sciences/The Royal Society 280 (1755), 20122889.

Moffett, A., Colucci, F., 2015. Co-evolution of NK receptors and HLA ligands in humans is driven by reproduction. Immunological Reviews 267 (1), 283–297.

Moore, C.B., John, M., James, I.R., Christiansen, F.T., Witt, C.S., Mallal, S.A., 2002. Evidence of HIV-1 adaptation to HLA-restricted immune responses at a population level. Science 296 (5572), 1439–1443.

Nei, M., Gu, X., Sitnikova, T., 1997. Evolution by the birth-and-death process in multigene families of the vertebrate immune system. Proceedings of the National Academy of Sciences of the United States of America 94 (15), 7799–7806.

Nielsen, N., Odum, N., Urso, B., Lanier, L.L., Spee, P., 2012. Cytotoxicity of CD56(bright) NK cells towards autologous activated $CD4^+$ T cells is mediated through NKG2D, LFA-1 and TRAIL and dampened via CD94/NKG2A. PloS One 7 (2), e31959.

Nolan, D., Gaudieri, S., Mallal, S., 2006. Host genetics and viral infections: immunology taught by viruses, virology taught by the immune system. Current Opinion in Immunology 18 (4), 413–421.

Ober, C., 1999. Studies of HLA, fertility and mate choice in a human isolate. Human Reproduction Update 5 (2), 103–107.

Olivares, M., Neef, A., Castillejo, G., Palma, G.D., Varea, V., Capilla, A., et al., 2015. The HLA-DQ2 genotype selects for early intestinal microbiota composition in infants at high risk of developing coeliac disease. Gut 64 (3), 406–417.

van Oosterhout, C., 2009. A new theory of MHC evolution: beyond selection on the immune genes. Proceedings Biological Sciences/The Royal Society 276 (1657), 657–665.

Parham, P., Moffett, A., 2013. Variable NK cell receptors and their MHC class I ligands in immunity, reproduction and human evolution. Nature Reviews Immunology 13 (2), 133–144.

Parham, P., Abi-Rached, L., Matevosyan, L., Moesta, A.K., Norman, P.J., Older Aguilar, A.M., et al., 2010. Primate-specific regulation of natural killer cells. Journal of Medical Primatology 39 (4), 194–212.

Parham, P., 2015. Co-evolution of lymphocyte receptors with MHC class I. Immunological Reviews 267 (1), 1–5.

Penman, B.S., Ashby, B., Buckee, C.O., Gupta, S., 2013. Pathogen selection drives nonoverlapping associations between HLA loci. Proceedings of the National Academy of Sciences of the United States of America 110 (48), 19645–19650.

Peppa, D., Gill, U.S., Reynolds, G., Easom, N.J., Pallett, L.J., Schurich, A., et al., 2013. Up-regulation of a death receptor renders antiviral T cells susceptible to NK cell-mediated deletion. The Journal of Experimental Medicine 210 (1), 99–114.

Pietra, G., Romagnani, C., Moretta, L., Mingari, M.C., 2009. HLA-E and HLA-E-bound peptides: recognition by subsets of NK and T cells. Current Pharmaceutical Design 15 (28), 3336–3344.

Pietra, G., Romagnani, C., Manzini, C., Moretta, L., Mingari, M.C., 2010. The emerging role of HLA-E-restricted $CD8^+$ T lymphocytes in the adaptive immune response to pathogens and tumors. Journal of Biomedicine & Biotechnology 2010, 907092.

Piontkivska, H., Nei, M., 2003. Birth-and-death evolution in primate MHC class I genes: divergence time estimates. Molecular Biology and Evolution 20 (4), 601–609.

Prugnolle, F., Manica, A., Charpentier, M., Guegan, J.F., Guernier, V., Balloux, F., 2005. Pathogen-driven selection and worldwide HLA class I diversity. Current Biology: CB 15 (11), 1022–1027.

Robinson, J., Halliwell, J.A., Hayhurst, J.D., Flicek, P., Parham, P., Marsh, S.G., 2015. The IPD and IMGT/HLA database: allele variant databases. Nucleic Acids Research 43 (Database issue), D423–D431.

Scher, J.U., Sczesnak, A., Longman, R.S., Segata, N., Ubeda, C., Bielski, C., et al., 2013. Expansion of intestinal Prevotella copri correlates with enhanced susceptibility to arthritis. eLife 2, e01202.

Taneja, V., 2014. Arthritis susceptibility and the gut microbiome. FEBS Letters 588 (22), 4244–4249.

Tomasec, P., Braud, V.M., Rickards, C., Powell, M.B., McSharry, B.P., Gadola, S., et al., 2000. Surface expression of HLA-E, an inhibitor of natural killer cells, enhanced by human cytomegalovirus gpUL40. Science 287 (5455), 1031.

Trowsdale, J., 2001. Genetic and functional relationships between MHC and NK receptor genes. Immunity 15 (3), 363–374.

Ulbrecht, M., Couturier, A., Martinozzi, S., Pla, M., Srivastava, R., Peterson, P.A., et al., 1999. Cell surface expression of HLA-E: interaction with human beta2-microglobulin and allelic differences. European Journal of Immunology 29 (2), 537–547.

Vider-Shalit, T., Fishbain, V., Raffaeli, S., Louzoun, Y., 2007. Phase-dependent immune evasion of herpesviruses. Journal of Virology 81 (17), 9536–9545.

Wang, E.C., McSharry, B., Retiere, C., Tomasec, P., Williams, S., Borysiewicz, L.K., et al., 2002. UL40-mediated NK evasion during productive infection with human cytomegalovirus. Proceedings of the National Academy of Sciences of the United States of America 99 (11), 7570–7575.

Watanabe, Y., Tokunaga, K., Geraghty, D.E., Tadokoro, K., Juji, T., 1997. Large-scale comparative mapping of the MHC class I region of predominant haplotypes in Japanese. Immunogenetics 46 (2), 135–141.

Watkins, D.I., McAdam, S.N., Liu, X., Strang, C.R., Milford, E.L., Levine, C.G., et al., 1992. New recombinant HLA-B alleles in a tribe of South American Amerindians indicate rapid evolution of MHC class I loci. Nature 357 (6376), 329–333.

Wilson, M.J., Torkar, M., Haude, A., Milne, S., Jones, T., Sheer, D., et al., 2000. Plasticity in the organization and sequences of human KIR/ILT gene families. Proceedings of the National Academy of Sciences of the United States of America 97 (9), 4778–4783.

Ziegler, A., Santos, P.S., Kellermann, T., Uchanska-Ziegler, B., 2010. Self/nonself perception, reproduction and the extended MHC. Self/Nonself 1 (3), 176–191.

Chapter 14

Human Life History Evolution: New Perspectives on Body and Brain Growth

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INTRODUCTION

Humans are primates but differ importantly from other species—even the great apes—in body, brain, and life history traits. Allometry, the study of how body size scales nonlinearly with various traits, reveals broad interspecies patterns in a wide variety of physiological and life-history traits across vertebrate taxa (Calder, 1986) including mammals and subgroups of mammals (Promislow and Harvey, 1990). For example, among primate species, body size scales consistently with both longevity and age at sexual maturation (Fig. 14.1A and B). Despite numerous individual species exceptions, there exists a clear pattern that larger mammal species reach sexual maturity later, have slower rates of reproduction, and live longer compared with smaller species.

Mechanisms underlying these relationships remain obscure, however. Early hypotheses attributing these relationships to either whole-body metabolic rate or to metabolic rate of specific organs such as the brain (Sacher, 1959; Mallouk, 1975) have failed as complete explanations (Austad and Fischer, 1991; Speakman, 2005). Not only that, consideration of actual energy expenditure rather than basal energy expenditure reveals somewhat different relationships between body size and life history traits (Speakman, 2005). Nonetheless, energetics is likely to play some role in allometric relationships.

Similar patterns, albeit with quantitative variation, are seen within mammalian orders as well as across them. Compared with other mammalian orders, primates are characterized by their exceptionally slow life history and long life even after accounting for body size. Although primates are not *the* longest-lived mammalian order in either absolute or relative terms, primates are certainly *among* the longest-lived (Austad and Fischer, 1992). Without question, primates have the largest brains among mammalian orders, adjusting for body size (Eisenberg, 1981). In fact, it is their combination of relatively large brains and long life that largely drives theories of the causal relationship among relative brain size and long life (Sacher, 1959; Mallouk, 1975). Primates may also be the slowest to reach sexual maturity among all mammals for their size.

How does the human life history fit into the general mammalian and primate patterns? Are we as unique as we imagine or do we happen to be little more than a large bodied, large brained, fully bipedal mammal? Or, more specifically, how different are human life histories from one that might be expected from a great ape of our size? If we are different, what unique selective pressures may have made us so? These are the questions that inform the first part of this chapter. The second part examines cell and genomic features of brain development, and the role of the human APOE allele system, which is uniquely human among all primates examined.

MAMMALIAN PATTERNS

Because so many biological variables correlate with mammalian body mass, and because these relationships tend to be linear on log−log plots (Calder, 1986), a reasonable way to compare species that differ in size is to remove the effects of size by using the ratios of the actual variable of interest to that expected from regressions of the log−log plots of the variable of interest versus body size across an entire group. This is analogous to the analysis of regression residuals. For example, encephalization quotient (EQ) is the ratio of actual brain size to that expected for an average mammal of the same body size (Jerison, 1973).

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00014-4

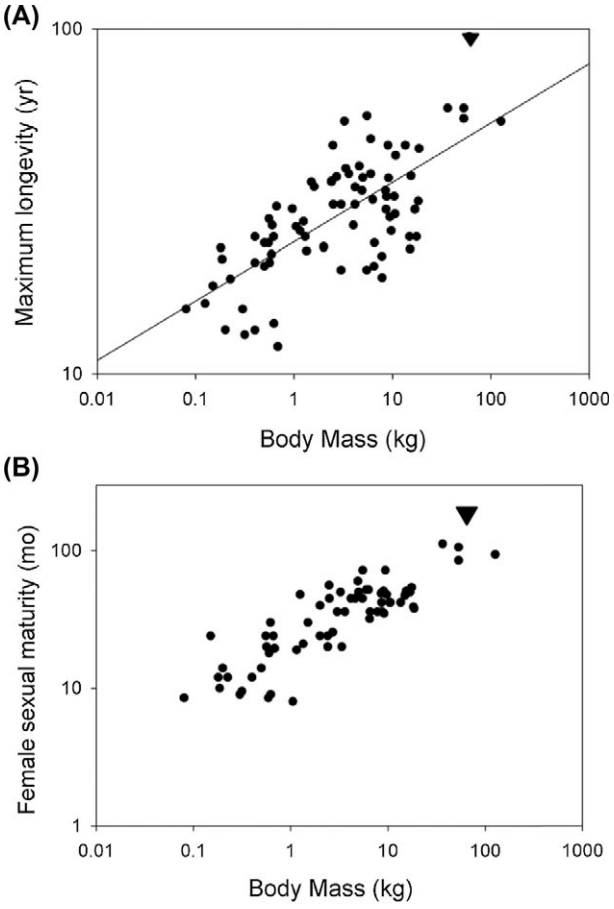

FIGURE 14.1 Primate body size, longevity, and age of female sexual maturity. Note that because all primate longevity records come from relatively small sample sizes (a few dozen to a few thousand) whereas there are millions of human longevity records, and because human environments, food, and health maintenance are much more carefully monitored than for captive primates, human longevity is set to 90 years rather than the actual verified human longevity record of 122 years. Modern human, large triangle. (A) Maximum longevity versus body mass ($r^2 = 0.49$, $p < 0.001$). (B) Female sexual maturity versus body mass ($r^2 = 0.74$, $p << 0.001$).

Correspondingly, the longevity quotient (LQ) is the ratio of actual longevity to that expected for a mammal of that size (Austad and Fischer, 1991). By these metrics, an average mammal species by definition has an EQ or LQ of 1 (Table 14.1). Those with greater than average brains or longevities have EQs or LQs greater than 1; those less than average are less than 1.

According to the EQ, primates generally have the largest brains of any mammalian order and humans have more than a threefold larger brain than any primate (Eisenberg, 1981) (Table 14.1; Fig. 14.2). Humans are not the longest-lived mammals, however, in either absolute or relative terms. At the least, fin whale and bowhead whales appear to substantially exceed human longevity (George et al., 1999), while at the other extreme relative to body size, bats are by far the longest-lived mammalian order (Austad and Fischer, 1991). Primates are the third longest-lived order after bats and monotremes (Table 14.1). Interestingly, primates are the only mammalian order which shows a positive relationship between EQ and LQ, suggesting the hypothesis that relative brain size has a unique role in primate longevity (Austad and Fischer, 1992). Although this crude analysis ignores potentially important differences of the relative size or synapse density of specific brain regions, the existence of the EQ–LQ relationship and its apparent uniqueness among mammals makes it worth exploring further.

TABLE 14.1 Longevity Quotient (LQ) and Encephalization Quotient (EQ) for Selected Mammalian Orders

Group	EQ	LQ	Number of Species
Chiroptera (bats)	0.94	3.52	64
Monotremes (platypus and echnidas)	0.83	2.68	3
Primates	2.54	2.28	82
Rodents	1.03	0.99	134
Artiodactyls (deer, gazelle, antelope, etc.)	0.84	0.85	101
Marsupials (pouched mammals)	0.61	0.83	66

Data for EQ from Eisenberg, J.F., 1981. The Mammalian Radiations. University of Chicago Press, Chicago. LQs calculated from data in *AnAge: The Animal Ageing and Longevity Database.*

PRIMATE PATTERNS

As stated previously, body mass is positively associated with both longevity and age of sexual maturity (puberty) in primates (Fig. 14.1) and across all mammals. In fact, there is an excellent correlation between the time taken to reach sexual maturity and the length of adult life both in the primate data set analyzed here ($r = 0.76$, $p < 0.001$) as for mammals generally. We suggest that there are shared molecular pacemaker(s) of growth and longevity, which involve anabolic pathways including insulin-like growth factors and mTOR (Wood et al., 2014; Johnson et al., 2013).

So far, we have not invoked aging, the rate of physiological decline with advancing age, but rather have focused on longevity. Species longevity, in this case as in most comparative studies, is defined by the maximum longevity record for a species. Although longevity data are available for hundreds of species, this metric is not optimal from a demographic or statistical standpoint, particularly when it is

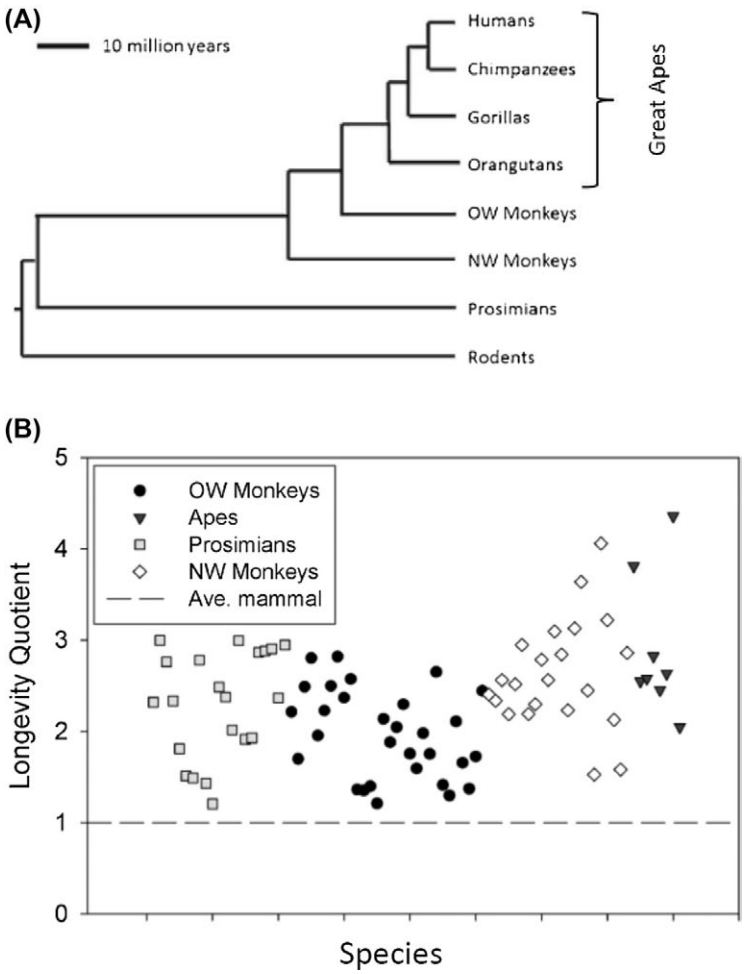

FIGURE 14.2 The effect of phylogeny of longevity quotients (LQs) in primates. (A) General phylogeny of the great apes and other major primate groups. (B) LQ among distinct primate clades. See text for explanation.

based on small samples (Promislow, 1993). The relationship between aging and longevity is complex, particularly when for species comparisons. Most, but not all, of our longevity records come from captive populations in zoos or research facilities. Animals in captive populations, of course, reach states of advanced decrepitude that animals facing the challenges of nature never reach, in which a minority dies of senescence or defined aging-related causes. Thus captive longevity might seem a particularly valuable measure of aging. While generally that is true, it is also true that the quality of captive husbandry varies considerably among species. Adequate diets, favorable psychosocial environments, exposure to infectious diseases, and variable criteria for euthanasia are all factors that affect species in captivity in not particularly predictable ways. To illustrate how these factors might affect primates, we note that a comparison of zoo records as of the years 1982 and 1999 shows that in one-third of primate genera, maximum longevity increased by nearly half over this time interval, and in 12% of genera, maximum longevity more than doubled (Austad, 2006). For these reasons, we focus on the actual data available (longevity) rather than speculate about underlying physical decline (aging).

Are there phylogenetic trends among primates in either age of sexual maturity or longevity? The higher order outlines of primate phylogeny have been reasonably settled for nearly a decade (Fig. 14.2A), although details particularly within the prosimians (lemurs, lorises, and galagos, as used here) still need to be fully worked out (Fabre et al., 2009; Perelman et al., 2011; Pozzi et al., 2014). One can approach this issue by using a "quotient" approach as shown earlier to account for differences in body mass. Using a sexual maturity quotient (SMQ) derived only from primate body size−sexual maturity regression, it turns out that there is a pattern in the age of sexual maturity with prosimians maturing earlier than average primates (SMQ = 0.84), Old World monkeys maturing at about an average primate age (SMQ = 1.02),

and New World monkeys and great apes maturing later than average (SMQ = 1.26 and 1.37, respectively).

The LQs for primates (Fig. 14.2B) were calculated relative to all mammals with the exceptions of the bats and marsupials, two groups which do not show clear and consistent relationships between size and longevity (Austad and Fischer, 1991). As is clear from the figure, all primates are longer lived than expected for "average" mammals, that is, all LQs are greater than 1. Surprisingly, the range of LQs in the prosimians is virtually identical to that of the Old World monkeys. In fact, two lemur species, *Cheirogaleus medius* (fat-tailed dwarf lemur) and *Eulemur mongoz* (mongoose lemur) are longer lived for their body size than any Old World monkey. Similarly surprising is that New World monkeys have a broader spread of LQs than any other group and, with the exception of modern humans, live as long or longer than apes (Fig. 14.2B). In fact, the white-headed capuchin (*Cebus capucinus*) is the only primate besides humans that lives more than four times as long as predicted by its body size. We note in passing that this species also has an exceptionally large brain for its size even by primate standards (Eisenberg, 1981); likewise, the white-handed gibbon (*Hylobates lar*), the ape with the second highest LQ after humans, has the second highest ape EQ.

HUMANS

Humans diverged from a common ancestor with chimpanzees roughly 6–8 million years ago. Since that imprecisely known time, humans and chimpanzees have also diverged in body size, developmental rate, age at sexual maturity, interbirth interval, aging rate, and longevity (Robson and Wood, 2008). What can we glean about the pattern, pace, or mechanism(s) of divergence in these life history traits from existing ape species or the hominid paleontological record?

Comparisons among great apes are often presented in the form of Table 14.2, with single species values for each trait of interest. Major efforts have gone into producing tables like this, which except for the longevity of nonhumans, are compiled from years of detailed field observations on natural primate populations. Longevity in this table is the longest-lived *captive* individual of the species. Human data in Table 14.2 come from modern hunter-gatherer and foraging populations. Still, collapsing these variables into a single number for each species disguises sufficient variation due to genetic and environmental heterogeneity, nutrient availability, energy balance, social and environmental stresses, etc., and many of these species differences may be considerably less clear than the raw averages suggest. For instance, among six populations of chimpanzees, median interbirth interval (IBI) spanned from 5.25 to 6.58 years (25% difference); the youngest female to give birth in a population ranged from 9.5 to 14.1 years (48%); and the oldest to give birth ranged from 40.6 to 55 years (35%) (Thompson et al., 2007). Human and chimpanzee populations also vary widely within each species for ages of sexual maturation (Table 14.2 footnotes a,b,c).

Given this variation, the great apes are surprisingly similar in their life histories with long IBIs from extended weaning periods. Chimpanzees reach menarche a bit earlier than humans and have their first live birth sooner (Table 14.2). The interval between menarche and first live birth is referred to as adolescent sterility or subfertility (Ashley Montague, 1939; Alberts et al., 2013) and is likely to be an overestimate of physical capability in humans because of cultural variations in the time of marital consummation (Mukherjee et al., 1996; Michael Gurven, personal communication). Additionally, humans continue to grow after menarche with a slower pelvic maturation (Abitbol, 1996; Berge, 1998; Bogin, 1999), which makes early age childbirth more difficult for humans than great

TABLE 14.2 Life History Variables of Female Great Apes

Species	Body Mass (kg)	EQ	Sexual Maturity (y)	First Birth (y)	Gestation (d)	Weaning (y)	IBI (y)	Longevity (y)
Orangutan (*Pongo* sp.)	37.8	1.7	15.4	7.0	260	7.0	8.1	59
Gorilla (sp.)	95.2	1.6	10.0	6.5	255	4.1	4.4	55
Bonobo (*Pan paniscus*)	33.4	2.3	14.2	9.0	244	4.5	6.3	55
Chimpanzee (Pan troglodytes)[a]	35.4	2.3	13.3	11.3	225	4.5	5.7	59
Modern human (*Homo sapiens*)[b,c]	45.5	7.5	19.5	14.0	270	2.8	3.7	85

EQ, Encephalization quotient; *IBI*, interbirth interval.
[a] *Pusey (1990), Adams Hillard (2014), and Wallis (1997).*
[b] *Gurven et al. (2012).*
[c] *Hawkes and Smith (2010)* and *Atsalis and Videan (2009).*
Adapted and updated from Robson, S.L., Wood, B., 2008. Hominin life history: reconstruction and evolution. Journal of Anatomy 212, 394–425; Emery–Thompson et al. (2007), AnAge: Animal Aging Database.

apes. The human pelvis has complex growth trajectories differing from chimpanzees, which Berge (1998) describes as "heterochronic," ie, differences in timing relative to our ancestor that include a late growth phase synchronized with the adolescent growth spurt. Other examples of heterochrony relative to the chimpanzee include the skull morphology and patterns of gene expression in the brain, as discussed later in this chapter. Reconstruction of australopithecine pelves suggested human-like obstetrical mechanics (Berge, 1998; Berge and Goularas, 2010). Humans have more prolonged and dangerous labor than chimpanzees, with intense social support unique to our species. We wonder if novel social support for mothers and children had begun before genus *Homo*.

Longevity appears similar among great apes except humans who live substantially longer than any other species. Moreover, humans have a unique postmenopausal life phase (Alberts et al., 2013). Notably, the general mammalian trend of longer life, later maturity, and slower reproductive rate with increasing size vanishes among the great apes. The largest species with the smallest relative brain size (gorillas) has the earliest age at maturity, the second largest with the biggest brain (humans) has the fastest reproductive rate, and the species (again, humans) with the fastest reproductive rate lives the longest. Thus it is not tenable to make predictions about life history traits in the great apes from body size alone.

Yet body size is one of the few indications we have of the pace and pattern of evolution since our divergence from chimpanzees as all other human species are extinct. For extinct human species, evidence is limited to that available from skeletons and associated artifacts such as coprolites. We now have complete genome sequences from both Neandertal and Denisovan humans (Paabo, 2015); while these remarkable data have not yet yielded much on comparative life history traits, they give convincing evidence of past interbreeding among these three species.

Skeletal remains can yield some information on age-at-death which might indicate the relative longevities of past human populations. Most analyses of age distribution by skeletal analysis paleodemography concluded that ancestral humans were considerably shorter lived than modern hunter-gatherer and foraging societies (Lovejoy et al., 1977; Bocquet-Appel and Masset, 1996). For instance, from 1300 well-preserved skeletons of a largely foraging population of Americans from 1000 years ago, life expectancy at birth was ~20 years and at age 15 years was ~19 years, with <3% of individuals surviving to age 50 years (Lovejoy et al., 1977). For comparison, modern hunter-gatherer and foraging groups have a life expectancy at birth of ~30 years and at age 15 years of ~20–40 years (Gurven and Kaplan, 2007). While ages up through 20–30 years are considered reliable, later ages are less certain (Konigsberg and Hermann, 2006; Hoppa and Vaupel, 2002). Another problem is the uneven preservation of remains, particularly of infants. These wide variations make it difficult to assess life expectancy, even in the ancient Roman world, which is well documented for so many other aspects of life (Parkin, 2003). There are similar problems in demographic studies of modern preliterate hunter-gatherers and foragers, which are relict populations living in marginal habitats. Still, the extensive and consistent data from living populations can give some idea of the longevity of preagricultural modern humans.

We face a far greater challenge in understanding the demography of earlier human species, however. One approach to approximately relative longevity among populations in the distant past is to estimate the OY ratio, that is the ratio of old (ie, sexually mature, not old in the sense of senescence) to young (sexually immature) individuals, although this can be confounded by differences in reproductive rate (Caspari and Lee, 2004). On this admittedly rough evidence, Australopithecines appear shorter lived, that is, have a higher ratio of preadult to adult skeletons, than early *Homo*. According to the same criterion, early *Homo* appears shorter lived than Neandertals, and Neandertals appear shorter lived than modern humans in the past 50,000 years. Based on the present types of evidence, we do not expect soon, if ever, to know when and how the differences between chimpanzee and human reproductive rates arose.

The history of adult human body size is complex and of interest on its own, specifically because of what it may indicate about ecological role, nutritional stress, and infectious diseases (Ruff, 2002). Prior to the appearance of our genus around 2 million years ago, early hominins were about the size of chimpanzees, although with different body proportions likely due to differences in locomotor habit. Even the early members of the genus *Homo* were not much smaller than modern humans. About 500,000 years ago, humans increased in size, growing to roughly ~10% larger in body mass than today. However, about 50,000 years ago, size began declining (Ruff et al., 1997), accelerating in many but not all populations with the development of agriculture in the past 10,000 years. In the past 150 years, with more reliable and nutritionally complete food available, body size has again begun to increase. The questions to be answered therefore are why the genus *Homo* grew larger than its ancestral genera, what was responsible for the further increase in size beginning 500,000 years ago, and what caused the decrease in size in the Upper Paleolithic. Changes over this time scale undoubtedly reflect genetic changes due to ecological variables such as climate, predators, prey density, and so forth—a topic which would be excessively speculative and beyond our scope.

Patterns of sexual size dimorphism among extinct hominins and has not been extensively explored and is potentially of considerable interest in understanding the ecology and/or mating systems. Australopithecines exhibited sexual

size dimorphism even greater than chimpanzees but without the same dimorphism in canine tooth size (Ruff, 2002). Increased body size and canine tooth dimorphism are generally considered reliable signs of increased sexual selection via male−male competition. The pattern of size dimorphism without dentition dimorphism is therefore puzzling and one wonders whether it might signal that teeth had ceased to be the major weapon of combat in Australopithecines. By the emergence of *Homo,* mean body size had increased at the same time that size dimorphism had decreased, implying that there had been a considerably bigger increase in female compared to male size. It is tempting to speculate that a relatively larger increase in size in females might have had something to do with changes in reproductive patterns. Perhaps bigger mothers were better able to care for multiple dependent children as the IBI was reduced? We do not know when the sex difference in brain size evolved, which is minimal in chimpanzees (Leigh, 2004).

Body size reduction began after 50,000 years ago, reaching the present size in association with the development of agriculture ~10,000 years ago (Ruff et al., 1997; Formicola, 2003). This trend has been traditionally attributed to a variety of factors, including less nutritionally complete diets, periodic famine, higher density populations, greater socioeconomic stratification, and increases in infectious diseases during development. While this is a compelling scenario with abundant evidence for post−Medieval Europe (Fogel, 2004), there was also a simultaneous reduction in body size in Australia where the indigenous population never developed agriculture or a truly urban life. Therefore, the appearance of agriculture and its sequelae cannot be a complete explanation of this pattern (Walker et al., 2006).

The increase in body size since 1800 is a component of what Robert Fogel calls the "technophysio" evolution of the 20th century also has its interest (Fogel and Costa, 1997). The height increase began more than a century ago in conjunction with the diminishing mortality from infections, long before antibiotics (Crimmins and Finch, 2006). With a diminishing load of childhood infections, adult height increased correspondingly, as seen in several European populations during the later 19th century (Crimmins and Finch, 2006). In earlier days, even those who survived childhood disease still incurred energy drains that impaired growth. For example, in some developing countries, adult height varies inversely with the frequency of childhood diarrhea (Finch, 2007, pp. 267−268). Growth is stunted because of energy deficits from impaired digestion and nutrient absorption (Lutter et al., 1989). Fever, which is also common in highly infected areas is energetically costly, and can increase basal metabolism 25%−50% (Finch, 2007, p. 56). In the 21st century, the height-mortality-longevity relationships show intriguing complexity. On one hand, cardiovascular disease varies inversely with adult height in several large populations (Batty et al., 2009; Nüesch et al., 2015). On the other hand, longevity showed the opposite trend of "shorter live longer" in several other populations (Samaras, 2013; He et al., 2014). This is also true for domestic dog breeds (Patronek et al., 1997; Creevy et al., 2016). Our era of minimal infectious burden with high levels of insulin resistance may comprise a pathophysiology of development and aging new to human biology. We have much to learn!

Interesting differences in height have emerged within modern nations. In the mid-19th century, Caucasian Americans were taller than the Australians, Canadians, and any of the countries of Europe (Komlos and Lauderdale, 2007). For instance, Americans were more than 9 cm taller than the Dutch at this time. Body size is less variable across national boundaries as food has remained superabundant in North America and Western Europe since the mid-20th century, public health measures have improved with more hygienic food and water, antibiotics and vaccines have been developed to work against numerous childhood diseases, and medical treatment has become more sophisticated. But there have been some strange reversals. By the end of the 20th century, Americans were no longer close to the tallest people. The Dutch now are about 5 cm taller than Americans, and are now the tallest people among developed countries. The exact reasons for the Dutch height surge are not clear; we wonder which direction will longevity proceed. Americans have also become relatively shorter lived compared to Western Europe since the middle of the 20th century.

BRAIN EVOLUTION

The human brain is unique among primates for its large size relative to body mass (Table 14.2; Bienvenu et al., 2011; Hanson et al., 2014), but also for its risk of Alzheimer's disease (AD) (Finch and Austad, 2015). Human brain-aging changes at later ages, with or without AD, are more severe than in chimps and other primates at advanced ages beyond the mean lifespan in captivity (Finch and Austad, 2014). Many primates show qualitatively similar, progressive deposition of amyloid β-peptide aggregates as diffuse extracellular deposits and as cerebrovascular amyloid angiopathy. Hyperphosphorylated tau also shows increase in neurons of aging monkeys. However, no aging primate has shown the human clinical AD level of severe neurodegeneration in the pathways for declarative memory that depend on reciprocal connections of the frontal neocortex to the hippocampus. While more exacting microscopic analysis is needed, we provisionally conclude that AD is unique to the human brain.

Further insight comes from brain evolutionary changes inferred from brain imaging by computed tomography (CT)

TABLE 14.3 Human Versus Chimpanzee Brain Ontogeny and Female Reproduction

	Cortical Synapse Density Maximum[a]	Puberty, Early Stage[b]	First Live Birth[b]	White Matter Myelin Maturation[c]	Caloric Production Value[d]	Menopause[e,f]
Chimpanzee	1	8	13	15	6	50
Human	5	8	18	30	30	50

[a] *Liu et al. (2012).*
[b] *Pusey (1990), Adams Hillard (2014),* and *Wallis (1997).*
[c] *Bartzokis et al. (2003)* and *Miller et al. (2012).*
[d] *Gurven et al. (2012).*
[e] *Hawkes and Smith (2010)* and *Atsalis and Videan (2009).*
[f] *Herndon et al. (2012).*

and magnetic resonance imaging (MRI) of humans and great apes; from gene expression profiles of humans and great ape brain; from DNA of great apes and fossils of human ancestor; and from cranial fossils. The richest insights are from modern genomes which show major changes in the developmental schedule of gene expression. We start with findings on brain morphology. This fragmentary evidence does not yet inform how or why humans uniquely evolved AD.

Besides our threefold larger brains, we differ from chimpanzees in the relative size of particular regions of cortical and subcortical regions (Bienvenu et al., 2011; Semendeferi et al., 2011). The olfactory bulb and cribriform plate are disproportionately larger (Bastir et al., 2011) and cortical gyri are deeper and more complex (Chen et al., 2013; Rilling, 2014). MRI scans of a large sample of chimpanzee brains adjusted for size showed relative enlargement of frontal cortex regions and amygdala, but relative shrinkage of the visual cortex (Aldridge, 2011). Structural MRI with diffusion tensor imaging (DTI) identified human cortical neuron tracts that differ from chimpanzees; of particular interest are tract differences in the speech areas of humans (Broca's and Wernicke's areas) (Zhang et al., 2013). At the cellular level, neuronal columns in the B10 region of the prefrontal cortex are narrower in humans than in great apes and with more space between columns (Semendeferi et al., 2001, 2011). These structural findings suggest region-specific changes in function.

Developmental heterochrony is notable, with much later maturation of adult synapse density and maximum size (Table 14.3). Correspondingly, myelination of white matter tracts continues to increase in frontal lobes long after sexual maturity, peaking as late as age 40 years. In contrast, chimpanzee brain myelination is complete by age 10–15 years. These differences match the much slower social maturation of humans than chimpanzees. Human male hunter-gatherers and others living in preindustrial societies typically do not achieve maximum skills until after age 25 years; maximum food production measured as calories is reached even later (Schniter et al., 2015; Gurven et al., 2007). We may ask if there is any relationship of prolonged brain maturation to later life neurodegeneration.

GENE EXPRESSION

Benchmark studies from the Max Planck Institute for Evolutionary Anthropology in Leipzig have identified gene expression patterns with major quantitative differences in human and chimp brain during postnatal development. Sets of genes show heterochronic expression for mRNA levels relative to sexual maturation (Somel et al., 2009; Liu et al., 2012). One set of synaptic genes showed remarkable region-specific differences in timing in human, chimpanzee, and macaque; these heterochronic genes are implicated in the delayed maturation of pyramidal neuron synapse density in prefrontal cortex of humans versus chimpanzees. A subset of these genes is regulated by the *MEF2A* promoter, which mediates neuron-specific expression. Intriguingly, the *MEF2A* promoter has an excess of single nucleotide polymorphisms (SNPs) relative to chimpanzee and Neandertal, suggesting that genes in this heterochronic module have evolved in the last 300,000 years. This report did not clarify if these changes resulted in multiple alleles. As discussed later in this chapter, the *APOE* gene, which influences pyramidal cortical neuron synapses and risk of AD, evolved novel alleles within this time frame.

The little we know about internal brain structures of early humans suggests changes in taste and smell perception. Endocrania showing the base of the brain surface indicate the sizes of olfactory bulbs and the temporal lobes, while the size of the cribriform plate through which the olfactory nerves pass into the bulbs gives a measure of these tracts (Bastir et al., 2010, 2011). Endocranial geometry had nonoverlapping principal components for archaic *Homo* versus Neandertal and modern humans, with 12% increase in the cribriform plate and olfactory bulbs. DNA analysis also indicates changes in olfaction. Relative to chimps, humans have lost 36 functional olfactory genes

through premature stop codons. Denisovan and Neandertal DNA show further gene loss (Hughes et al., 2014), which may be consistent with the smaller olfactory bulbs of Neandertals (Bastir et al., 2011). The receptor for bitter taste *TAS2R38* evolved three alleles in humans which are absent from Denisovans, WHO had the ancestral chimpanzee nucleotide in positions of the modern alleles (Perry et al., 2015). The loss of taste and smell sensitivity in AD has not been associated with any of these alleles.

Denisovans, ancestral by about 600,000 years, have other genes relevant to brain evolution that differ in coding from humans. Meyer et al. (2012) identified coding differences from modern humans in *KATNA1* and *SLITRK1*, for neurite outgrowth; *ARHGAP32* and *HTR2B*, synaptic transmission; *ASDL* and *CNTNAP2,* associated with autism. Further, Zhou et al. (2015) analyzed genomes of different ethnicities from the 1000 Genomes Project with new information on neolithic specimens. Genes related to brain cells showed changes that were dated to two periods: 400,000 ybp archaic *Homo* (*AUTS2, SLTM*, associated with autism; *RFN180* which regulates MAO-B, a key enzyme of monoamine metabolism) and ca. 50−150,000 ybp in early *Homo sapiens* (*SPON1, MAPT, SORL1, ELAVL4*, *SNCA,* neuronal genes). These authors speculated on the relation of these genes to AD with a model of gene cross-talk with hubs at the amyloid precursor protein (APP) and MAPT which codes for tau, a protein hyperphosphorylated in AD. We are cautious about such models because these genes are expressed brain wide and with no specificity for the regional specificity of AD neurodegeneration. Nonetheless, the evolutionary timing of these genes remains relevant to the subtle regional differences that define the human brain.

A set of noncoding regions (ncHAR) characterized by accelerated changes in humans have developmental enhanced activity in embryonic mouse brains. The first such identified is expressed in Cajal-Retzius neurons during human cortex development and has excess A/T and G/C conversions suggestive of GC-biased gene conversion (Pollard et al., 2006). Of great interest, about 8% of mutations in ncHARs arose within 1 million years (Burbano et al., 2012).

Besides these candidates in human brain evolution, we would include APOE, which has allelic variants that influence the risk of AD as well as altering the development of brain regions affected during AD.

APOE ALLELES

Humans are unique among primates in having multiple APOE alleles in which *APOE3* is the most prevalent (55−90%), followed by *E4* (5−35%), and *E2* (<10%). The risk of AD progressively declines in the order of E4>E3>E2 (Liu et al., 2013; Cacciottolo et al., 2016; Table 14.4). Nonetheless, 50% of AD patients do not carry *APOE4*, while 30% of *APOE4* carriers do not develop AD. For AD risk, *APOE4* can be considered "semi-dominant".

The *APOE3* allele is estimated to have spread in ancestral humans about 225,000 ybp, approximating the earliest anatomically modern *H. sapiens*, while *APOE2* is more recent, perhaps just before the first northward migration from Africa (Fullerton et al., 2000). Chimpanzees and mice have a single APOE isoform with the human pathogenic *APOE4* signature of two arginines (R) and positions 112 and 158. The different lipid binding affinity of *APOE4* is associated with higher blood levels of cholesterol (Mahley et al., 2009). The shared presence of R61 in Denisovans and human *APOE4* implies that *APOE4* is the ancestral isoform. However, chimpanzees and mice differ from humans by threonine at position 61, which was shown by genetic engineering to convert lipid binding to *APOE3*-like (Raffai et al., 2001). Of relevance to AD, APOE isoforms bind to human APP with allele-specific affinities that modulate Aβ production (Theendakara et al., 2013).

APOE also has unusual features in DNA methylation. The exon specifying the APOE isoforms has an unusual "CpG island" rare in coding regions that is shared with

TABLE 14.4 Apolipoprotein E Residues for Human Alleles and Ancestors

	Position 61	Position 112	Position 158	# CpGs in Allele Specifying Site
Human E2	R	C	C	2
Human E3	R	C	R	3
Human E4	R	R	R	4
Denisovan	R	R	R	4
Chimpanzee	T	R	R	4
Mouse	T	R	R	4

C, Cysteine; *R,* arginine; *T,* threonine (McIntosh et al., 2012). Note also that this order also represents a linear series in the number of total cysteines at 112 and 158 (Leuthold et al., 2013; Peterson et al., 2015). Thus, there are four cysteines per mole in E2/E2, three in E2/E3, two in E3/E3, one E3/E4, and zero in E4/E4; and reciprocally for arginine.

the chimpanzee (Yu et al., 2013). Intriguingly, at each step in APOE evolution, one CpG was lost during the coding changes; coincidentally, these transitions are represented in the abbreviation: *APOE4* with four CpGs; *APOE3* with three CpGs; and *APOE2* with two CpGs (Table 14.3). The methylation of APOE varies by brain region and cell type, and can influence transcription in transfection studies (Yu et al., 2013). However, the levels of APOE methylation did not correlate with APOE mRNA in human frontal cortex (Yu et al., 2013; Foraker et al., 2015). Individual cell-type data may be more informative because whole brain-region RNA cannot resolve cell-specific expression.

We may anticipate information on APOE methylation for Denisovans and other human ancestors. Because cytosine spontaneously deaminates postmortem to thymine, the C:T ratio can be calibrated to estimate for archaic DNA premortem methylation (Gokhman et al., 2014). APOE merits further inquiry because the differentially methylated regions of modern humans include genes associated with brain disease−related genes shared with Denisovans and Neandertals. Intriguingly, 184 genes with identical protein sequences in humans and chimpanzees have major differences in promoter methylation; APOE was not mentioned (Hernando-Herraez et al., 2015).

Not only does the ancestral *APOE4* allele increase vulnerability to AD, as the most prevalent risk factor, *APOE4* also modulates brain development, resistance to mental stress, and vulnerability to traumatic brain injury. Of major relevance to brain development, human *APOE3* is more neurotrophic than *E4* and has more efficient lipid delivery (Bellosta et al., 1995; Pitas et al., 1998). An MRI observational study of normal children showed that the entorhinal cortex was consistently thinner into adolescence in *APOE4* versus *APOE3* carriers (Shaw et al., 2007). A thinner temporal cortex was also found in neonatal *APOE4* carriers (Knickmeyer et al., 2014) and in Vietnam veterans (VETSA) aged 51−59 years (Kremen et al., 2013). Because of selective neurodegeneration in this brain region during early stages of AD, the thinner entorhinal cortex implies a smaller neuronal reserve in *APOE4* carriers. These APOE allele effects are regionally specific. For example, the hippocampus which receives projections from the entorhinal cortex and also damaged during AD, did not show any size differences by APOE allele in two studies (Kremen et al., 2013; Khan et al., 2014). Two MRI studies show fine structure differences of *APOE4* in healthy adults with regional specificity, in white matter diffusivity (Westlye et al., 2012) and in resting fMRI (Trachtenberg et al., 2012). Brain synchronous neural interaction during magnetoencephalography, a measure of functional connectivity, also varied in healthy adults with the *APOE4* allele dose, or number of APOE cysteine residues (Table 14.2 footnote) (Leuthold et al., 2013). Synapse-level effects are shown in transgenic mice: *APOE4* mice have pyramidal neurons with fewer dendritic spines (Wang et al., 2005) and altered excitatory synaptic transmission (Klein et al., 2014), relative to *APOE3* mice. Information on APOE2 in neuronal function will be forthcoming.

Resistance to stress is also decreased by *APOE4*. Posttraumatic stress disorder (PTSD) in association with combat stress was up to twofold more prevalent in US veterans of the Vietnam and Iraq conflicts with *APOE4* dose effects (Lyons et al., 2013; Peterson et al., 2015). While the contribution of direct head injury was not defined in PSTD outcome, traumatic brain injury has worse outcomes in *APOE4* carriers, eg, with greater cognitive impairments and brain amyloid load (Li et al., 2015). Given evidence for head injury in the Paleolithic fossil record (Coqueugniot et al., 2014; Wu et al., 2011), the ancestral *APOE4* would appear maladaptive to young adults. However, *APOE4* may be adaptive for infections as hypothesized by Martin (1999). For Brazilian slum children with diarrhea, *APOE4* carriers had better cognitive responses to micronutrient supplementation than the *APOE*3 carriers (Oriá et al., 2010; Mitter et al., 2012). Thus, under conditions of infection that differ from modern healthier populations, *APOE4* could be advantageous for brain development. This association is also shown in the resistance of malnourished mice to cryptosporidial infections, a common cause of diarrhea, in which the *APOE4* mice grew best (Azevedo et al., 2014). Other examples are described by Finch and Martin (2016). Thus, emergence of *APOE3* about 225,000 years ago represented selection for its advantages to brain development and survival to neurotrauma. *APOE2*, the newest allele, may have been adaptive to later-life brain health by further reducing AD risk. The persistence of *APOE4* as a minor allele in all modern populations could represent balancing selection for resistance to infection.

Returning to the prior discussion of evolving brain genes, we suggest that the APOE alleles may be a partner at the protein level by its modulation of neurite outgrowth. To explore these ideas further, the Finch lab made a mouse with targeted replacement of the chimpanzee APOE gene. Preliminary data show that chimpanzee APOE resembles human *APOE4* more than *APOE3* in support of neurite outgrowth (Cacciottollo et al., 2013). These experiments confirmed the Mahley group findings that human *APOE3* is more neurotrophic than E4, cited previously. Thus, we must consider other differences between human and chimpanzee APOE. Notably, of the eight residues that show evidence of positive selection in human APOE, half (4) of these residues are in their lipid-binding C-terminus (Vamathevan et al., 2008). The undefined influence of these other amino acid differences in lipid binding could also influence lipophilic steps in host defense.

Analyses of Caucasian humans have identified a second genetic locus, translocase of mitochondrial membrane 40 (*TOMM40*), closely linked to *APOE*, in which alleles with an expanded region of poly T repeats is associated with increased predictability of age of onset of AD and also has been linked to Parkinson's disease (Gottschalk et al., 2014). Whether *TOMM40* also has alleles with this repeat in chimpanzees will be fascinating to discover. Thus far, sufficient chimpanzee genomes to assess this possibility have not been sequenced.

PROSPECTUS

Human evolutionary biology has entered a new era in three major domains: the availability of DNA sequence data from fossil DNA, including gene variants; species comparisons in patterns of gene expression during development; and deeper knowledge of preindustrial life history for human forager-farmers. The present survey of these domains shows a great potential redefining of what it means to be human. We anticipate neurobiological findings on the brain systems that enable our unique multigenerational and multigender cooperativity; on the genes that enable our unique postreproductive life phase; and on the genes that promote neurodegenerative processes that are absent from other great apes.

ACKNOWLEDGMENTS

The authors are grateful for support from the NIH (Caleb Finch: AG05142, AG-040683, and AG026572; Steve Austad: AG037962 and R24 OD010933). They appreciate encouragement by the Center for Academic Research and Training in Anthropogeny (CARTA).

REFERENCES

Abitbol, M.M., 1996. The shapes of the female pelvis: contributing factors. The Journal of Reproductive Medicine 41, 242–250.

Adams Hillard, P.J., 2014. Menstruation in adolescents: what do we know? and what do we do with the information? Journal of Pediatric and Adolescent Gynecology 27, 309–319.

Alberts, S.C., Altmann, J., Brockman, D.K., Cords, M., Fedigan, L.M., Pusey, A., Stoinski, T.S., Strier, K.B., Morris, W.F., Bronikowski, A.M., 2013. Reproductive aging patterns in primates reveal that humans are distinct. Proceedings of the National Academy of Sciences of the United States of America 110, 13440–13445.

Aldridge, K., 2011. Patterns of differences in brain morphology in humans as compared to extant apes. Journal of Human Evolution 60, 94–105.

AnAge: The Animal Ageing and Longevity Database. http://genomics.senescence.info/species/.

Ashley-Montague, M.F., 1939. Adolescent sterility. The Quarterly Review of Biology 14, 13–34.

Atsalis, S., Videan, E., 2009. Reproductive aging in captive and wild common chimpanzees: factors influencing the rate of follicular depletion. American Journal of Primatology 71, 271–282.

Austad, S.N., 2006. Patterns in mammalian aging: demography and evolution. In: Robine, J.-M., Crimmins, E., Horiuchi, S., Yi, Z. (Eds.), Longevity, Individual Life Duration, and the Growth of the Oldest-Old Population. Springer, Dordrecht, Netherlands, pp. 43–55.

Austad, S.N., Fischer, K.E., 1991. Mammalian aging, metabolism, and ecology: evidence from the bats and marsupials. The Journal of Gerontology 46, B47–B53.

Austad, S.N., Fischer, K.E., 1992. Primate longevity: its place in the mammalian scheme. American Journal of Primatology 28, 251–261.

Azevedo, O.G., Bolick, D.T., Roche, J.K., Pinkerton, R.F., Lima, A.A., Vitek, M.P., Warren, C.A., Oriá, R.B., Guerrant, R.L., 2014. Apolipoprotein E plays a key role against cryptosporidial infection in transgenic undernourished mice. PLoS One 9, e89562.

Bartzokis, G., Cummings, J.L., Sultzer, D., Henderson, V.W., Nuechterlein, K.H., Mintz, J., 2003. White matter structural integrity in healthy aging adults and patients with Alzheimer disease: a magnetic resonance imaging study. Archives of Neurology 60, 393–398.

Bastir, M., Rosas, A., Gunz, P., Peña-Melian, A., Manzi, G., Harvati, K., Kruszynski, R., Stringer, C., Hublin, J.J., 2011. Evolution of the base of the brain in highly encephalized human species. Nature Communications 2, 588.

Bastir, M., Rosas, A., Stringer, C., Cuétara, J.M., Kruszynski, R., Weber, G.W., Ross, C.F., Ravosa, M.J., 2010. Effects of brain and facial size on basicranial form in human and primate evolution. Journal of Human Evolution 58, 424–431.

Batty, G.D., Shipley, M.J., Gunnell, D., Huxley, R., Kivimaki, M., Woodward, M., Lee, C.M., Smith, G.D., 2009. Height, wealth, and health: an overview with new data from three longitudinal studies. Economics and Human Biology 7, 137–152.

Bellosta, S., Nathan, B.P., Orth, M., Dong, L.M., Mahley, R.W., Pitas, R.E., 1995. Stable expression and secretion of apolipoproteins E3 and E4 in mouse neuroblastoma cells produces differential effects on neurite outgrowth. The Journal of Biological Chemistry 270, 27063–27071.

Berge, C., 1998. Heterochronic processes in human evolution: an ontogenetic analysis of the hominid pelvis. American Journal of Physical Anthropology 105, 441–459.

Berge, C., Goularas, D., 2010. A new reconstruction of Sts 14 pelvis (*Australopithecus africanus*) from computed tomography and three-dimensional modeling techniques. Journal of Human Evolution 58, 262–272.

Bienvenu, T., Guy, F., Coudyzer, W., Gilissen, E., Roualdès, G., Vignaud, P., Brunet, M., 2011. Assessing endocranial variations in great apes and humans using 3D data from virtual endocasts. American Journal of Physical Anthropology 145, 231–246.

Bocquet-Appel, J.P., Masset, C., 1996. Paleodemography: expectancy and false hope. American Journal of Physical Anthropology 99, 571–583.

Bogin, B., 1999. Evolutionary perspective on human growth. Annual Review of Anthropology 28, 109–153.

Burbano, H.A., Green, R.E., Maricic, T., Lalueza-Fox, C., de la Rasilla, M., Rosas, A., Kelso, J., Pollard, K.S., Lachmann, M., Paabo, S., 2012. Analysis of human accelerated DNA regions using archaic hominin genomes. PLoS One 7 (3), e32877.

Cacciottolo, M., Christensen, A., Moser, A., Liu, J., Pike, C.J., Smith, C., LaDu, M.J., Sullivan, P.M., Morgan, T.E., Dolzhenko, E., Charidimou, A., Wahlund, L.O., Wiberg, M.K., Shams, S., Chiang, G.C., Alzheimer's Disease Neuroimaging Initiative, Finch, C.E., 2016. The APOE4 allele shows opposite sex bias in microbleeds and Alzheimer's disease of humans and mice. Neurobiology of Aging 37, 47–57.

Cacciottollo, M.S.P., Morgan, T.E., Finch, C.E., June 3–4, 2013. Chimpanzee apolipoprotein E comparison with human apoE3 and -E4 for effect on neuronal outgrowth. In: 4th Annual Symposium: "ApoE, ApoE Receptors, and Neurodegeneration". Georgetown University, Washington, DC.

Calder, W.A.I., 1986. Size, Function, and Life History. Mineola, New York, Dover.

Caspari, R., Lee, S.H., 2004. Older age becomes common late in human evolution. Proceedings of the National Academy of Sciences of the United States of America 101, 10895–10900.

Chen, X., Errangi, B., Li, L., Glasser, M.F., Westlye, L.T., Fjell, A.M., Walhovd, K.B., Hu, X., Herndon, J.G., Preuss, T.M., Rilling, J.K., 2013. Brain aging in humans, chimpanzees (*Pan troglodytes*), and rhesus macaques (*Macaca mulatta*): magnetic resonance imaging studies of macro- and microstructural changes. Neurobiology of Aging 34 (10), 2248–2260.

Coqueugniot, H., Dutour, O., Arensburg, B., Duday, H., Vandermeersch, B., Tillier, A.M., 2014. Earliest cranio-encephalic trauma from the Levantine Middle Palaeolithic: 3D reappraisal of the Qafzeh 11 skull, consequences of pediatric brain damage on individual life condition and social care. PLoS One 9, e102822.

Creevy, K.E., Austad, S.N., Hoffman, J.M., O'Neill, D.G., Promislow, D.E., 2016. The Companion Dog as a Model for the Longevity Dividend. Cold Spring Harbor Perspectives in Medicine 6 (1). pii: a026633.

Crimmins, E.M., Finch, C.E., 2006. Infection, inflammation, height, and longevity. Proceedings of the National Academy of Sciences of the United States of America 103, 498–503.

Eisenberg, J.F., 1981. The Mammalian Radiations. University of Chicago Press, Chicago.

Fabre, P.H., Rodrigues, A., Douzery, E.J., 2009. Patterns of macroevolution among Primates inferred from a supermatrix of mitochondrial and nuclear DNA. Molecular Phylogenetics and Evolution 53, 808–825.

Finch, C.E., 2007. The Biology of Human Aging. Inflammation, Nutrition, and Aging in the Evolution of Lifespans. Academic Press, San Diego.

Finch, C.E., Austad, C.E., 2014. Evolution of human brain aging and neurological diseases. Annual Review of Gerontology and Geriatrics 159–170 (Chapter 5).

Finch, C.E., Austad, C.E., 2015. Commentary: is Alzheimer disease uniquely human? Neurobiology of Aging 36, 553–555.

Finch, C.E., Martin, G.M., 2016. Dementias of the Alzheimer type: views through the lens of evolutionary biology suggest amyloid-driven brain aging is a trade-off with host defence. In: Alvergne, A. (Ed.), Evolutionary Thinking in Medicine: From Research to Policy and Practice. Springer (in press).

Fogel, R.W., Costa, D.L., 1997. A theory of technophysio evolution, with some implications for forecasting population, health care costs, and pension costs. Demography 34, 49–66.

Fogel, R.W., 2004. The Escape from Hunger and Premature Death, 1700–2100. Cambridge University Press, Cambridge, UK.

Foraker, J., Millard, S.P., Leong, L., Thomson, Z., Chen, S., Keene, C.D., Bekris, L.M., Yu, C.E., 2015. The APOE gene is differentially methylated in Alzheimer's disease. Journal of Alzheimer's Disease 48 (3), 745–755.

Formicola, V., 2003. More is not always better: Trotter and Gleser's equations and stature estimates of Upper Paleolithic European samples. Journal of Human Evolution 45, 239–243.

Fullerton, S.M., Clark, A.G., Weiss, K.M., Nickerson, D.A., Taylor, S.L., Stengård, J.H., Salomaa, V., Vartiainen, E., Perola, M., Boerwinkle, E., Sing, C.F., 2000. Apolipoprotein E variation at the sequence haplotype level: implications for the origin and maintenance of a major human polymorphism. American Journal of Human Genetics 67, 881–900.

George, J.C., Bada, J., Zeh, J., Scott, L., Brown, S.E., O'Hara, T., Suydam, R., 1999. Age and growth estimates of bowhead whales (*Balaena mysticetus*) via aspartic acid racemization. Canadian Journal of Zoology 77, 571–580.

Gokhman, D., Lavi, E., Prüfer, K., Fraga, M.F., Riancho, J.A., Kelso, J., Pääbo, S., Meshorer, E., Carmel, L., 2014. Reconstructing the DNA methylation maps of the Neandertal and the Denisovan. Science 344, 523–527.

Gottschalk, W.K., Lutz, M.W., He, Y.T., Saunders, A.M., Burns, D.K., Roses, A.D., Chiba-Falek, O., 2014. The broad impact of TOM40 on neurodegenerative diseases in aging. Journal of Parkinson's Disease and Alzheimer's Disease 1. pii:12.

Gurven, M., Kaplan, H., 2007. Longevity among hunter-gatherers: a cross-cultural examination. Population and Development Review 33, 321–365.

Gurven, M., Kaplan, H., Supa, A.Z., 2007. Mortality experience of Tsimane Amerindians of Bolivia: regional variation and temporal trends. American Journal of Human Biology 19, 376–398.

Gurven, M., Stieglitz, J., Hooper, P.L., Gomes, C., Kaplan, H., 2012. From the womb to the tomb: the role of transfers in shaping the evolved human life history. Experimental Gerontology 47, 807–813.

Hanson, K.L., Hrvoj-Mihic, B., Semendeferi, K., 2014. A dual comparative approach: integrating lines of evidence from human evolutionary neuroanatomy and neurodevelopmental disorders. Brain, Behavior and Evolution 84, 135–155.

Hawkes, K., Smith, K.R., 2010. Do women stop early? Similarities in fertility decline in humans and chimpanzees. Annals of the New York Academy of Sciences 204, 43–53.

He, Q., Morris, B.J., Grove, J.S., Petrovitch, H., Ross, W., Masaki, K.H., Rodriguez, B., Chen, R., Donlon, T.A., Willcox, D.C., Willcox, B.J., 2014. Shorter men live longer: association of height with longevity and FOXO3 genotype in American men of Japanese ancestry. PLoS One 9, e94385.

Hernando-Herraez, I., Garcia-Perez, R., Sharp, A.J., Marques-Bonet, T., 2015. DNA Methylation: Insights into Human Evolution. PLOS Genetics 11 (12), e1005661.

Herndon, J.G., Paredes, J., Wilson, M.E., Bloomsmith, M.A., 2012. Menopause occurs late in life in the captive chimpanzee (*Pan troglodytes*). Age 34, 1145–1156.

Hoppa, R.D., Vaupel, J.W., 2002. The Rostock Manifesto for Paleodemography. In: Hoppa, R.D., Vaupel, J.W. (Eds.), Paleodemography. Age Distributions from Skeletal Samples. Cambridge University Press.

Hughes, G.M., Teeling, E.C., Higgins, D.G., 2014. Loss of olfactory receptor function in hominin evolution. PLoS One 9, e84714.

Jerison, H.J., 1973. Evolution of the Brain and Intelligence. Academic Press, New York.

Johnson, S.C., Rabinovitch, P.S., Kaeberlein, M., 2013. mTOR is a key modulator of ageing and age-related disease. Nature 493, 338–345.

Khan, W., Giampietro, V., Ginestet, C., Dell'Acqua, F., Bouls, D., Newhouse, S., Dobson, R., Banaschewski, T., Barker, G.J., Bokde, A.L., Büchel, C., Conrod, P., Flor, H., Frouin, V., Garavan, H., Gowland, P., Heinz, A., Ittermann, B., Lemaître, H.,

Nees, F., Paus, T., Pausova, Z., Rietschel, M., Smolka, M.N., Ströhle, A., Gallinat, J., Westman, E., Schumann, G., Lovestone, S., Simmons, A., IMAGEN consortium, 2014. No differences in hippocampal volume between carriers and non-carriers of the ApoE ε4 and ε2 alleles in young healthy adolescents. Journal of Alzheimer's Disease 40, 37–43.

Klein, R.C., Acheson, S.K., Mace, B.E., Sullivan, P.M., Moore, S.D., 2014. Altered neurotransmission in the lateral amygdala in aged human apoE4 targeted replacement mice. Neurobiology of Aging 35, 2046–2052.

Knickmeyer, R.C., Wang, J., Zhu, H., Geng, X., Woolson, S., Hamer, R.M., Konneker, T., Lin, W., Styner, M., Gilmore, J.H., 2014. Common variants in psychiatric risk genes predict brain structure at birth. Cerebral Cortex 24, 1230–1246.

Komlos, J., Lauderdale, B.E., 2007. The mysterious trend in American heights in the 20th century. Annals of Human Biology 34, 206–215.

Konigsberg, L.W., Hermann, N.P., 2006. The osteological evidence for human longevity in the recent past. In: Hawkes, K., Paine, R.R. (Eds.), The Evolution of the Human Life History. Sante Fe, NM, pp. 267–306.

Kremen, W.S., Fennema-Notestine, C., Eyler, L.T., Panizzon, M.S., Chen, C.H., Franz, C.E., Lyons, M.J., Thompson, W.K., Dale, A.M., 2013. Genetics of brain structure: contributions from the Vietnam era twin study of aging. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics 162B, 751–761.

Leigh, S.R., 2004. Brain growth, life history, and cognition in primate and human evolution. American Journal of Primatology 62, 139–164.

Leuthold, A.C., Mahan, M.Y., Stanwyck, J.J., Georgopoulos, A., Georgopoulos, A.P., 2013. The number of cysteine residues per mole in apolipoprotein E affects systematically synchronous neural interactions in women's healthy brains. Experimental Brain Research 226, 525–536.

Li, L., Bao, Y., He, S., Wang, G., Guan, Y., Ma, D., Wu, R., Wang, P., Huang, X., Tao, S., Liu, Q., Wang, Y., Yang, J., 2015. The association between apolipoprotein E and functional outcome after traumatic brain injury: a meta-analysis. Medicine (Baltimore) 94 (46), e2028.

Liu, C.C., Kanekiyo, T., Xu, H., Bu, G., 2013. Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nature Reviews Neurology 9, 106–118.

Liu, X., Somel, M., Tang, L., Yan, Z., Jiang, X., Guo, S., Yuan, Y., He, L., Oleksiak, A., Zhang, Y., Li, N., Hu, Y., Chen, W., Qiu, Z., Pääbo, S., Khaitovich, P., 2012. Extension of cortical synaptic development distinguishes humans from chimpanzees and macaques. Genome Research 22, 611–622.

Lovejoy, C.O., Meindl, R.S., Pryzbeck, T.R., Barton, T.S., Heiple, K.G., Kotting, D., 1977. Paleodemography of the Libben site, Ottawa Oounty, Ohio. Science 198, 291–293.

Lutter, C.K., Mora, J.O., Habicht, J.P., Rasmussen, K.M., Robson, D.S., Sellers, S.G., Super, C.M., Herrera, M.G., 1989. Nutritional supplementation: effects on child stunting because of diarrhea. American Journal of Clinical Nutrition 50, 1–8.

Lyons, M.J., Genderson, M., Grant, M.D., Logue, M., Zink, T., McKenzie, R., Franz, C.E., Panizzon, M., Lohr, J.B., Jerskey, B., Kremen, W.S., 2013. Gene-environment interaction of ApoE genotype and combat exposure on PTSD. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics 162B, 762–769.

Mahley, R.W., Weisgraber, K.H., Huang, Y., 2009. Apolipoprotein E: structure determines function, from atherosclerosis to Alzheimer's disease to AIDS. Journal of Lipid Research 50 (Suppl.), S183–S188.

Mallouk, R.S., 1975. Longevity in vertebrates is proportional to relative brain weight. Federation Proceedings 34, 2102–2103.

Martin, G.M., 1999. APOE alleles and lipophylic pathogens. Neurobiology of Aging 20, 441–443.

McIntosh, A.M., Bennett, C., Dickson, D., Anestis, S.F., Watts, D.P., Webster, T.H., Fontenot, M.B., Bradley, B.J., 2012. The apolipoprotein E (APOE) gene appears functionally monomorphic in chimpanzees (Pan troglodytes). PLoS One 7 (10), e47760.

Meyer, M., Kircher, M., Gansauge, M.T., Li, H., Racimo, F., Mallick, S., Schraiber, J.G., Jay, F., Prüfer, K., de Filippo, C., Sudmant, P.H., Alkan, C., Fu, Q., Do, R., Rohland, N., Tandon, A., Siebauer, M., Green, R.E., Bryc, K., Briggs, A.W., Stenzel, U., Dabney, J., Shendure, J., Kitzman, J., Hammer, M.F., Shunkov, M.V., Derevianko, A.P., Patterson, N., Andrés, A.M., Eichler, E.E., Slatkin, M., Reich, D., Kelso, J., Pääbo, S., 2012. A high-coverage genome sequence from an archaic Denisovan individual. Science 338 (6104), 222–226.

Miller, D.J., Duka, T., Stimpson, C.D., Schapiro, S.J., Baze, W.B., McArthur, M.J., Fobbs, A.J., Sousa, A.M., Sestan, N., Wildman, D.E., Lipovich, L., Kuzawa, C.W., Hof, P.R., Sherwood, C.C., 2012. Prolonged myelination in human neocortical evolution. Proceedings of the National Academy of Sciences of the United States of America 109, 16480–16485.

Mitter, S.S., Oriá, R.B., Kvalsund, M.P., Pamplona, P., Joventino, E.S., Mota, R.M., Gonçalves, D.C., Patrick, P.D., Guerrant, R.L., Lima, A.A., 2012. Apolipoprotein E4 influences growth and cognitive responses to micronutrient supplementation in shantytown children from northeast Brazil. Clinics (Sao Paulo) 67, 11–18.

Mukherjee, S., Bhattacharya, B.N., Singh, K.K., 1996. Distribution of time of first birth in presence of social customs regulating physical separation and coital frequency. Mathematical Biosciences 131, 1–21.

Nüesch, E., Dale, C., Palmer, T.M., White, J., Keating, B.J., van Iperen, E.P., Goel, A., Padmanabhan, S., Asselbergs, F.W., EPIC-Netherland Investigators, Verschuren, W.M., Wijmenga, C., Van der Schouw, Y.T., Onland-Moret, N.C., Lange, L.A., Hovingh, G.K., Sivapalaratnam, S., Morris, R.W., Whincup, P.H., Wannamethee, G.S., Gaunt, T.R., Ebrahim, S., Steel, L., Nair, N., Reiner, A.P., Kooperberg, C., Wilson, J.F., Bolton, J.L., McLachlan, S., Price, J.F., Strachan, M.W., Robertson, C.M., Kleber, M.E., Delgado, G., März, W., Melander, O., Dominiczak, A.F., Farrall, M., Watkins, H., Leusink, M., Maitland-van der Zee, A.H., de Groot, M.C., Dudbridge, F., Hingorani, A., Ben-Shlomo, Y., Lawlor, D.A., UCLEB Investigators, Amuzu, A., Caufield, M., Cavadino, A., Cooper, J., Davies, T.L., IN Day, Drenos, F., Engmann, J., Finan, C., Giambartolomei, C., Hardy, R., Humphries, S.E., Hypponen, E., Kivimaki, M., Kuh, D., Kumari, M., Ong, K., Plagnol, V., Power, C., Richards, M., Shah, S., Shah, T., Sofat, R., Talmud, P.J., Wareham, N., Warren, H., Whittaker, J.C., Wong, A., Zabaneh, D., Davey Smith, G., Wells, J.C., Leon, D.A., Holmes, M.V., Casas, J.P., 2015. Adult height, coronary heart disease and stroke: a multi-locus Mendelian randomization meta-analysis. International Journal of Epidemiology. pii: dyv074.

Oriá, R.B., Patrick, P.D., Oriá, M.O., Lorntz, B., Thompson, M.R., Azevedo, O.G., Lobo, R.N., Pinkerton, R.F., Guerrant, R.L., Lima, A.A., 2010. ApoE polymorphisms and diarrheal outcomes in Brazilian shanty town children. Brazilian Journal of Medical and Biological Research 43, 249–256.

Paabo, S., 2015. The diverse origins of the human gene pool. Nature Reviews Genetics 16, 313–314.

Parkin, T.G., 2003. Old Age in the Roman World. Baltimore, MD.

Patronek, G.J., Waters, D.J., Glickman, L.T., 1997. Comparative longevity of pet dogs and humans: implications for gerontology research. Journals of Gerontology Series A: Biological Sciences and Medical Sciences 52, B171–B178.

Perelman, P., Johnson, W.E., Roos, C., Seuanez, H.N., Horvath, J.E., Moreira, M.A., Kessing, B., Pontius, J., Roelke, M., Rumpler, Y., Schneider, M.P., Silva, A., O'Brien, S.J., Pecon-Slattery, J., 2011. A molecular phylogeny of living primates. PLoS Genetics 7, e1001342.

Perry, G.H., Kistler, L., Kelaita, M.A., Sams, A.J., 2015. Insights into hominin phenotypic and dietary evolution from ancient DNA sequence data. Journal of Human Evolution 79, 55–63.

Peterson, C.K., James, L.M., Anders, S.L., Engdahl, B.E., Georgopoulos, A.P., 2015. The number of cysteine residues per mole in apolipoprotein E is associated with the severity of PTSD re-experiencing symptoms. Journal of Neuropsychiatry and Clinical Neurosciences 27, 157–161.

Pitas, R.E., Ji, Z.S., Weisgraber, K.H., Mahley, R.W., 1998. Role of apolipoprotein E in modulating neurite outgrowth: potential effect of intracellular apolipoprotein E. Biochemical Society Transactions 26, 257–262.

Pollard, K.S., Salama, S.R., Lambert, N., Lambot, M.A., Coppens, S., Pedersen, J.S., Katzman, S., King, B., Onodera, C., Siepel, A., Kern, A.D., Dehay, C., Igel, H., Ares Jr., M., Vanderhaeghen, P., Haussler, D., 2006. An RNA gene expressed during cortical development evolved rapidly in humans. Nature 443, 167–172.

Pozzi, L., Hodgson, J.A., Burrell, A.S., Sterner, K.N., Raaum, R.L., Disotell, T.R., 2014. Primate phylogenetic relationships and divergence dates inferred from complete mitochondrial genomes. Molecular Phylogenetics and Evolution 75, 165–183.

Promislow, D.E., 1993. On size and survival: progress and pitfalls in the allometry of life span. The Journal of Gerontology 48, B115–B123.

Promislow, D.E.L., Harvey, P.H., 1990. Living fast and dying young: a comparative analysis of life history variation among mammals. Journal of Zoology 220, 417–437.

Pusey, A.E., 1990. Behavioural changes at adolescence in chimpanzees. Behavior 115, 203–246.

Raffai, R.L., Dong, L.M., Farese Jr., R.V., Weisgraber, K.H., 2001. Introduction of human apolipoprotein E4 "domain interaction" into mouse apolipoprotein E. Proceedings of the National Academy of Sciences of the United States of America 98, 11587–11591.

Rilling, J.K., 2014. Comparative primate neuroimaging: insights into human brain evolution. Trends in Cognitive Sciences 18, 46–55.

Robson, S.L., Wood, B., 2008. Hominin life history: reconstruction and evolution. Journal of Anatomy 212, 394–425.

Ruff, C., 2002. Variation in human body size and shape. Annual Review of Anthropology 31, 211–232.

Ruff, C.B., Trinkaus, E., Holliday, T.W., 1997. Body mass and encephalization in Pleistocene Homo. Nature 387, 173–176.

Sacher, G.A., 1959. Relation of life span to brain weight and body weight in mammals. In: Wolstenholme, G.E.W., O'Connor, M. (Eds.), CIBA Foundation Colloquia on Ageing, vol. 5, pp. 115–133. London, Churchill.

Samaras, T.T., 2013. Shorter height is related to lower cardiovascular disease risk – a narrative review. Indian Heart Journal 65, 66–71.

Schniter, E., Gurven, M., Kaplan, H.S., Wilcox, N.T., Hooper, P.L., 2015. Skill ontogeny among Tsimane forager-horticulturalists. American Journal of Physical Anthropology 158, 3–18.

Semendeferi, K., Armstrong, E., Schleicher, A., Zilles, K., Van Hoesen, G.W., 2001. Prefrontal cortex in humans and apes: a comparative study of area 10. American Journal of Physical Anthropology 114, 224–241.

Semendeferi, K., Teffer, K., Buxhoeveden, D.P., Park, M.S., Bludau, S., Amunts, K., Travis, K., Buckwalter, J., 2011. Spatial organization of neurons in the frontal pole sets humans apart from great apes. Cerebral Cortex 21, 1485–1497.

Shaw, P., Lerch, J.P., Pruessner, J.C., Taylor, K.N., Rose, A.B., Greenstein, D., Clasen, L., Evans, A., Rapoport, J.L., Giedd, J.N., 2007. Cortical morphology in children and adolescents with different apolipoprotein E gene polymorphisms: an observational study. Lancet Neurology 6, 494–500.

Somel, M., Franz, H., Yan, Z., Lorenc, A., Guo, S., Giger, T., Kelso, J., Nickel, B., Dannemann, M., Bahn, S., Webster, M.J., Weickert, C.S., Lachmann, M., Pääbo, S., Khaitovich, P., 2009. Transcriptional neoteny in the human brain. Proceedings of the National Academy of Sciences of the United States of America 106, 5743–5748.

Speakman, J.R., 2005. Body size, energy metabolism and lifespan. Journal of Experimental Biology 208 (Pt 9), 1717–1730.

Theendakara, V., Patent, A., Peters Libeu, C.A., Philpot, B., Flores, S., Descamps, O., Poksay, K.S., Zhang, Q., Cailing, G., Hart, M., John, V., Rao, R.V., Bredesen, D.E., 2013. Neuroprotective sirtuin ratio reversed by ApoE4. Proceedings of the National Academy of Sciences of the United States of America 110, 18303–18308.

Thompson, M.E., Jones, J.H., Pusey, A.E., Brewer-Marsden, S., Goodall, J., Marsden, D., Matsuzawa, T., Nishida, T., Reynolds, V., Sugiyama, Y., Wrangham, R.W., 2007. Aging and fertility patterns in wild chimpanzees provide insights into the evolution of menopause. Current Biology 17, 2150–2156.

Trachtenberg, A.J., Filippini, N., Ebmeier, K.P., Smith, S.M., Karpe, F., Mackay, C.E., 2012. The effects of APOE on the functional architecture of the resting brain. Neuroimage 59, 565–572.

Vamathevan, J.J., Hasan, S., Emes, R.D., Amrine-Madsen, H., Rajagopalan, D., Topp, S.D., Kumar, V., Word, M., Simmons, M.D., Foord, S.M., Sanseau, P., Yang, Z., Holbrook, J.D., 2008. The role of positive selection in determining the molecular cause of species differences in disease. BMC Evolutionary Biology 8, 273.

Walker, R., Gurven, M., Hill, K., Migliano, A., Chagnon, N., De Souza, R., Djurovic, et al., 2006. Growth rates and life histories in twenty-two small-scale societies. American Journal of Human Biology 18, 295–311.

Wallis, J., 1997. A survey of reproductive parameters in the free-ranging chimpanzees of Gombe National Park. Journal of Reproduction and Fertility 109, 297–307.

Wang, C., Wilson, W.A., Moore, S.D., Mace, B.E., Maeda, N., Schmechel, D.E., Sullivan, P.M., 2005. Human apoE4-targeted replacement mice display synaptic deficits in the absence of neuropathology. Neurobiology of Disease 18, 390–398.

Westlye, L.T., Reinvang, I., Rootwelt, H., Espeseth, T., 2012. Effects of APOE on brain white matter microstructure in healthy adults. Neurology 79, 1961–1969.

Wood, A.R., Esko, T., Yang, J., Vedantam, S., Pers, T.H., Gustafsson, S., et al., 2014. Defining the role of common variation in the genomic and biological architecture of adult human height. Nature Genetics 46, 1173–1186.

Wu, X.J., Schepartz, L.A., Liu, W., Trinkaus, E., 2011. Antemortem trauma and survival in the late Middle Pleistocene human cranium from Maba, South China. Proceedings of the National Academy of Sciences of the United States of America 108, 19558–19562.

Yu, C.E., Cudaback, E., Foraker, J., Thomson, Z., Leong, L., Lutz, F., Gill, J.A., Saxton, A., Kraemer, B., Navas, P., Keene, C.D., Montine, T., Bekris, L.M., 2013. Epigenetic signature and enhancer activity of the human APOE gene. Human Molecular Genetics 22, 5036–5047.

Zhang, D., Guo, L., Zhu, D., Li, K., Li, L., Chen, H., Zhao, Q., Hu, X., Liu, T., 2013. Diffusion tensor imaging reveals evolution of primate brain architectures. Brain Structure and Function 218, 1429–1450.

Zhou, H., Matveev, R., Yu, Q., Khaitovich, P., Jin, L., Lachman, M., Stoneking, M., Fu, Q., Tang, K., 2015. A chronological atlas of natural selection in the human genome during the past half-million years. BioRxiv. http://dx.doi.org/10.1101/018929.

Chapter 15

Gorillas in Our Midst? Human Sexual Dimorphism and Contest Competition in Men

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INTRODUCTION

Around 500 BCE, the Carthaginian explorer Hanno the Navigator sailed south with a fleet of 60 ships along the northwest coast of Africa, encountering an island people he reported were comprised mostly of women. The men managed to escape, but Hanno's expedition captured three women who fought back so violently that they were executed by their abductors, their skins carried back to Carthage. Apparently oblivious to the hypocrisy, Hanno referred to these people as savages. His interpreters called them *Gorillai*, "tribe of hairy women" (Hanno, 1832). Over two millennia later, in 1847, Americans Thomas Savage and Jeffries Wyman borrowed this term when first describing the western gorilla (Conniff, 2009). Savage, Wyman, and the actions of Hanno's expedition were products of their times and easily strike the 21st century reader as racist and vile. We will revisit the human tendencies to classify others as in-group versus out-group, potentially regard out-group members as subhuman, and aggress against them, in our discussion of coalitional aggression in a later section.

Returning for the moment to gorillas, we note that research on these intelligent, elusive apes has revealed a wealth of information about their ecology and behavior. One of the most conspicuous aspects of gorilla social structure is that males aggressively defend groups of females from other males using their massive size, long canine teeth, and threat displays (Fossey, 1983; Maple and Hoff, 1982). Such traits are central to the behavioral repertoire of male gorillas, who experience what Charles Darwin termed *sexual selection*, a type of natural selection engendered by competition over mates (Andersson, 1994).

Since the publication of Darwin's *The Descent of Man* in 1871, a vast literature has accumulated demonstrating the salience of sexual selection in shaping the phenotypes of sexually reproducing organisms, including gorillas and humans. Sometimes referred to as "Darwin's other idea," sexual selection favors traits helpful in winning mating opportunities and is effectuated to varying degrees across species by a handful of mechanisms (Andersson, 1994). These mechanisms include *mate choice*, which favors traits desired by the opposite sex; *sexual coercion*, the use of force or threat against mates; *sperm competition*, the post-copulatory struggle for fertilization of ova that favors traits such as increased sperm production and motility; and *contest competition*, favoring traits that help win mates through same-sex physical contests and/or threatening displays directed at rivals.

Much research has focused on mate choice, though recent years have seen a reevaluation of sexual selection in humans with an increase in attention to contest competition, whose influence now seems to have been underestimated (eg, Carrier and Morgan, 2015; Hill et al., 2013; Puts, 2010, 2016; Puts et al., 2015; Scott et al., 2012). In this chapter, we consider data bearing on the influence of contest competition on men's phenotypes, but first we evaluate evidence for the overall intensity of sexual selection among ancestral men.

STRENGTH OF SEXUAL SELECTION IN MEN

A fundamental reality of reproduction in many sexually reproducing species is an asymmetry in parental

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00015-6

investment: one sex, usually females, invests more in producing and caring for offspring (Trivers, 1972). Women, for example, require approximately nine months for gestation, followed by a long period of lactation and childrearing, while a contrastingly small parental effort is required for men to reproduce (Eibl-Eibesfeldt, 1989; Geary, 2000). As a result, men have a higher potential reproductive rate (Clutton-Brock and Vincent, 1991), and in natural fertility populations, there are at all times more men available to mate than there are reproductively viable women (Trivers, 1972). This skews the operational sex ratio (OSR), the number of sexually active males per fecund female, in a way that tends across species to force males into competition for the relatively few available females (Clutton-Brock and Vincent, 1991; Emlen and Oring, 1977).

The *physiological* OSR, which includes all individuals capable of reproducing, can be distinguished from the *behavioral* OSR, which includes only those engaged in mating (Marlowe and Berbesque, 2012). This may be an important distinction because the amount of time individuals are typically eligible as mating partners may exert a greater effect on sexual selection than does the amount of time individuals are physiologically capable of reproducing (Kokko and Jennions, 2008; Kokko et al., 2012). The human behavioral OSR has been estimated to be 8.6, and the physiological OSR has been estimated to be 11.7 (Marlowe and Berbesque, 2012). Regardless of which measure is used, however, the human OSR falls below orangutans (OSR = 55.0) and gorillas (OSR = 83.8), which display the highest degrees of sexual dimorphism in the primate order, and above promiscuously mating chimpanzees (OSR = 4.5), which also exhibit substantial individual and coalitional contest competition, as well as a high degree of sperm competition (Mitani et al., 1996). Hence the human OSR indicates the opportunity for moderately strong sexual selection in men.

The intensity of sexual selection is also influenced by the spatial distribution of males and females, which affects whether mates can be monopolized. Across species, female reproduction is typically limited by access to food, whereas male reproduction is limited by access to mates. Hence, females generally distribute themselves according to resource availability, as well as predation risk, and males then distribute themselves according to the distribution of females (Lindenfors et al., 2004). If females are social or otherwise spatially clustered, then one or a few males may be capable of monopolizing multiple females, and competition to be one of the few breeding males will tend to be intense (Emlen and Oring, 1977). However, if female group sizes are large, then it may be infeasible for a smaller number of males to defend them from other males, and larger multimale/multifemale groups will emerge. Male mating competition is often intense in such species, frequently taking the form of male dominance hierarchies in which dominant males gain more mating opportunities, especially with estrous females. However, in primates, canine size dimorphism and body size dimorphism tend to be less extreme in multimale/multifemale species than in species with single-male polygyny (Clutton-Brock and Harvey, 1984), probably in part reflecting less intense sexual selection.

Although humans form large multimale/multifemale groups, the human mating system is not typical of such primates, as concealed ovulation prohibits males from attempting to monopolize estrous females (Gangestad and Thornhill, 2008; Puts et al., 2013). Perhaps as a consequence, within these larger groups are embedded smaller groups of individual males mated in relatively stable and exclusive relationships to one or more females. These mateships exhibit moderate polygyny. For example, on average, 21% of married women are married polygynously across forager societies, although the degree of polygyny varies substantially across cultures and ecological contexts (Marlowe and Berbesque, 2012). As in hamadryas baboons (Schreier and Swedell, 2009), males' proprietariness over their mates helps maintain these embedded "harems" (Daly and Wilson, 1988).

Males' ability to monopolize females may also be contingent on the dimensionality of the mating environment (Puts, 2010). Males may more effectively monopolize females in environments that are one-dimensional (eg, burrows or tunnels) or two-dimensional (eg, land or floors of bodies of water), as opposed to three-dimensional environments, such as air, open water, or trees, where the region that must be defended is larger, and there are many in-routes for sexually interloping males. As a result, compared to three-dimensional mating environments, terrestrial environments may favor greater physical competition for mates, as in terrestrially breeding seals (Stirling, 1975) and turtles (Berry and Shine, 1980) relative to aquatically breeding species. Hominins have evolved in a two-dimensional environment at least since the emergence of habitual bipedalism in *Australopithecus anamensis* roughly four million years ago (Harcourt-Smith, 2007). This shift in the human paleoenvironment likely played an influential role in shaping mating behavior in our lineage. In particular, the new terrestrial environment may have enabled ancestral males to restrict sexual access to mates to a degree that was infeasible in their more arboreal ancestors.

Male mating competition also tends to increase with reproductive variance among males compared to females (Bateman, 1948). In humans, male reproductive variance exceeds that of females but this difference is highly variable across populations (Brown et al., 2009). For example, reproductive maxima have been reported as 8 and 14 for women and 23 and 43 for men among two populations of lowland South American Indians (Chagnon, 1992; Salzano et al., 1967), an approximately three-fold increase among

males. However, the concentrations of wealth and power afforded by state-level societies have produced staggering reproductive variances. According to the Guinness Book of World Records, the largest number of children known to have been produced by a single woman is 69, while that for a man exceeds 1000 (Glenday, 2013). Men who are able to compete successfully for mates have the potential to produce a large number of offspring, whereas others may not reproduce at all. Women, by contrast, accrue less additional reproductive success from acquiring multiple mates—at most, they can reproduce approximately once per year, but interbirth intervals span several years in traditional societies (Blurton Jones, 1987).

It is thus unsurprising that societies allowing polygynous marriage are far more common in the ethnographic record than are those with only monogamous marriages (Murdock, 1967). Yet, even in societies with exclusively monogamous marriage, the mating system may nevertheless tend toward polygyny; men remarry (Buckle et al., 1996) and reproduce (Jokela et al., 2010) after divorce at higher rates than women (though see Borgerhoff Mulder, 2009), with reproductive variances comparable to those seen in societies with polygynous marriage (Brown et al., 2009). This pattern is not restricted to the West, the industrialized world, or the Global North—men exhibit greater reproductive variance than do women among some serially monogamous hunter-gatherers, as well (Hill and Hurtado, 1996).

The previously mentioned evidence suggests a robust potential for sexual selection in shaping men's anatomy and reproductive behavior. Women provide greater levels of parental investment through producing and rearing offspring, removing themselves from the mating pool for longer periods of time with each reproductive event. The consequent imbalance in the OSR predicts increased competition among males for mating opportunities. Men's potential to monopolize mates is reduced by women's aggregation into large groups but promoted by their terrestriality, which enables some men to defend multiple mates. As a result, men display greater reproductive variance than do women. These lines of evidence are consistent with a strong *potential* for sexual selection to shape men's phenotypes. However, sexual selection also requires nonrandom mating among men, such that men's phenotypes affect their mating opportunities. As we will now discuss, ancestral men appear to have won mates by developing traits that contributed to success in contest competition.

SELECTION FOR MALE CONTESTS

When evaluating the influence of past sexual selection on a trait, it is useful to consider several types of evidence (Table 15.1). First, high levels of sexual dimorphism suggest past sexual selection (Andersson, 1994; Darwin, 1871; Lande, 1980). Second, traits that function in mating competition are often costly to produce and maintain, and so often develop or increase in their expression at sexual maturity when they can begin to compensate for these costs. Third, if a trait affects success in one or more mechanisms of sexual selection (eg, by attracting mates or winning fights with same-sex competitors), then this suggests that the trait did so over its evolution. This may be demonstrated experimentally (eg, Andersson, 1982), or by providing correlational evidence that the trait influences success under a mechanism of sexual selection (eg, Schwagmeyer and Woontner, 1986). Fourth, if a trait affects mating success, then this indicates that it did so over its evolution. Again, experimental manipulations provide stronger evidence of causation (eg, Andersson, 1982), but correlational data can also provide evidence of a trait's influence on mating success and may have the advantage of increased ecological validity.

TABLE 15.1 Evidence of Past Sexual Selection on a Trait

- Sexually dimorphic
- Develops or increases in expression at sexual maturity
- Affects success in one or more mechanisms of sexual selection
- Affects mating success

None of these lines of evidence is sufficient by itself. For example, different ecological selection pressures such as niche partitioning can produce sexual dimorphisms, although this appears to be relatively rare (Andersson, 1994), and sexual selection may sometimes act similarly in the two sexes producing low sexual dimorphism (Hooper and Miller, 2008). In addition, if relevant aspects of the environment have changed, then a trait may currently influence mating success differently than it did ancestrally. However, in combination, these lines can provide strong evidence for past sexual selection. If a trait develops at sexual maturity, is sexually dimorphic, and appears to influence mating success through one or more mechanisms of sexual selection, then it is likely that the trait was shaped by sexual selection through these mechanisms.

Research exploring the influence of sexual selection on men's traits often emphasizes the role of female mate choice, but this emphasis may be based partly on misperceptions regarding the freedom with which women chose mates ancestrally (see, eg, Puts, 2010). Given the latitude with which women seem to choose mates in contemporary Western societies, it may surprise some readers that ancestral women probably experienced far less autonomy. For example, more than two-thirds of extant hunter-gatherer groups in a large sample had parentally arranged marriages (Apostolou, 2007), and while women may sometimes circumvent kin limitations on partner

choice (eg, via "mock bride theft"; Ayres, 1974), phylogenetic analyses suggest that family members influenced mating among the earliest members of our species (Walker et al., 2011). Moreover, constraints on female choice are imposed not only by kin but also by unrelated men via sexual coercion (Puts, 2016; Puts et al., 2015a), and especially by men's exclusion of male rivals by force or threat (eg, Hill et al., 2013).

Indeed, the weight of evidence suggests that many aspects of the human male phenotype are best explained by an evolutionary history of contest competition. Contests tend to produce several types of traits that aid in excluding same-sex competitors by force or threat, including behaviors such as same-sex aggression and threat displays, and anatomical traits such as large body size and anatomical weapons (Table 15.2). If any of these traits is present, then it is a good candidate to examine for evidence of having been shaped by sexual selection via contests. As we will see, men tend to exhibit all of the hallmarks of a species that has experienced an evolutionary history of male contest competition.

Same-Sex Aggression

Across cultures, men and boys are more physically aggressive than are girls and women (Archer, 2004; Ellis et al., 2008), and men's aggression peaks at the age of greatest mating competition (Archer, 2009). Murder in particular is overwhelmingly a male phenomenon. Men greatly outnumber women in both killing and being killed everywhere that homicide has been studied (Daly and Wilson, 1988), including both subsistence societies (Beckerman et al., 2009; Chagnon, 1988; Walker and Bailey, 2013) as well as industrialized Western nations (Daly and Wilson, 1990). For example, in the Yanomamo, horticulturalists living in parts of Brazil and Venezuela, Chagnon (1988) estimated violence to account for nearly one-third of male deaths, while Walker and Bailey (2013) found the mean percentage of violent deaths among 11 traditional lowland South American societies to be 30%. Males, moreover, accounted for 69% of all such deaths, with comparable figures seen across the societies in the sample. From a wide array of human populations, Daly and Wilson (1988) report 95% of same-sex killings to be perpetrated by men, even when war-related homicides are excluded from analysis. This sex difference holds across populations even as the number of homicides changes dramatically from one to another (Daly and Wilson, 1990). As Wright (1995, p. 72) has noted, "From an evolutionary point of view, the leading cause of violence is maleness."

TABLE 15.2 Traits Favored by Contest Competition

- Physical aggression
- Large body size
- Strength
- Weapons
- Behavioral displays of formidability
- Anatomical threat displays

Of course, a male bias in physical aggression and violence, especially a bias in male-on-male aggression and violence, is predicted from the hypothesis that ancestral men competed for mates via contest competition. Physical aggression may have helped men obtain or defend mates directly, for example, by killing or injuring a competitor attempting to win the same mate (Marlowe, 2004), or attempting to steal one's mate (Chagnon, 1992), but these may have more frequently been accomplished indirectly through the threat of physical harm (see later in this chapter).

Another possible set of behavioral adaptations that may allow males to remain physically aggressive during contests relates to pain thresholds and tolerance. Physical pain signals actual or potential tissue damage and can motivate withdrawal from a damaging situation and protection of a damaged body part (Lynn, 1984). However, withdrawing from injurious behavior imposes costs if the behavior is potentially fitness enhancing. In such situations, organisms face a tradeoff between avoiding tissue damage and missing opportunities to increase fitness. The relative weights of the associated costs and benefits will vary between individuals and across contexts. Given stronger sexual selection and greater reproductive variance among men compared to women, men are generally expected to engage in costlier, more injurious behaviors in contexts that can augment mating success, such as contest competition. Ancestral men who disengaged from or avoided contests may have suffered fewer injuries but left fewer offspring. The experience of less pain for a given stimulus may represent a proximate mechanism shaped by sexual selection to facilitate continued engagement in contests despite injury. If so, then men would be expected to exhibit less pain sensitivity and greater pain tolerance, perhaps especially in competitive contexts.

These predictions have been borne out. Relative to women, men can undergo more intense stimulation such as physical pressure on the body for longer periods of time before experiencing pain, they are able to tolerate more pain, and these effect sizes are moderate to large (Fillingim et al., 2009; Riley et al., 1998). Moreover, in one study, men experienced analgesia after competition against a same-sex competitor regardless of exercise, whereas women experienced analgesia only after exercise (Sternberg et al., 2001).

Anatomical Adaptations for Male Contests

While observational studies of aggression among primates provide the most direct evidence of contest competition, another relevant line of evidence concerns body size sexual

dimorphism. In a sample of 18 species of anthropoids representing 12 genera, Mitani et al. (1996) confirmed the relationship between body size dimorphism and OSR expected from sexual selection theory. In the human lineage, sexual size dimorphism exhibits great antiquity revealed through a large, albeit fragmentary, hominin fossil record dating back millions of years (Plavcan, 2012). Yet, research on levels of sexual dimorphism in earlier hominins is equivocal. For example, the best-represented fossil hominin, *Australopithecus afarensis*, which lived roughly 3–4 million years ago, has been alleged by some researchers (Gordon et al., 2008; Lockwood et al., 1996; McHenry, 1991), but not others (Reno and Lovejoy, 2015; Reno et al., 2010; Reno et al., 2003), to have exhibited a level of sexual dimorphism commensurate with that of extant gorillas and orangutans.

By the time of *Homo erectus*, whose existence covers most of the last 2 million years, sexual dimorphism had reached the approximate levels of modern *Homo sapiens* (Antón, 2003). Among modern humans, skeletal dimorphism is consistent with a primate species in which males are 45%–50% larger (Gordon et al., 2008). Compared to women, men possess 31%–43% more fat-free body mass (Lassek and Gaulin, 2009; Wells, 2012), 61% more muscle mass overall, and 75% more upper-body muscle mass (Abe et al., 2003; Lassek and Gaulin, 2009). As a result, the average man is stronger than 99.9% of women (Lassek and Gaulin, 2009).

Men with a masculine, muscular body shape have more sex partners (Frederick and Haselton, 2007; Hill et al., 2013; Lassek and Gaulin, 2009), particularly in short-term relationships (Rhodes et al., 2005), and begin having sex at an earlier age (Hughes and Gallup, 2003) than do less masculine men. Larger men, both in terms of height (Frederick and Jenkins, 2015; Mueller and Mazur, 2001) and body mass (Frederick and Jenkins, 2015), also report more sex partners. Although mating success does not necessarily translate into reproductive success among natural fertility populations, positive relationships have been observed between men's reproductive success and both height (Mueller and Mazur, 2001; Pawlowski et al., 2000) and physical prowess (Chagnon, 1988; Smith et al., 2003).

Men also appear designed to weather bodily insults, particularly to the head, which is disproportionately targeted (Shepherd et al., 1988) and injured (Carrier and Morgan, 2015) in fights. Brink et al. (1998) examined 2432 bodily injuries in 1156 men and 325 women in Denmark for a one-year period in the mid-1990s, reporting 69% to have been craniofacial, with injuries in both sexes tending to be produced by blunt force at close range. Indeed, sexual dimorphism in cranial robusticity may partly be attributable to physical violence among men, as features such as more robust mandibles and brow ridges may protect against catastrophic facial fractures (Carrier and Morgan, 2015; Puts, 2010). Women generally do not experience commensurate levels of physical aggression (Campbell, 2013; Daly and Wilson, 1988) and display less cranial robusticity and fewer cranial injuries (Carrier and Morgan, 2015; Shepherd et al., 1988).

Weapons Use

Contest competition often favors the evolution of anatomical weapons, such as antlers, horns, and, in primates, large canine teeth. Yet, compared with our closest living relatives, both men and women possess relatively small canines, and we lack substantial canine-size sexual dimorphism (Wood et al., 1991). Diminution in canine size and a departure from the CP_3 honing complex, a typical ape feature, begins with one of the earliest hominin candidates (7 to 6 Ma), *Sahelanthropus tchadensis* (Brunet et al., 2002), and continues through the Pliocene genera *Ardipithecus* (Suwa et al., 2009) and *Australopithecus* (White et al., 2000) to *Homo* after 2.5 Ma (Suwa et al., 2009).

One hypothesis for reduction in canines and other skeletal features related to biting is that canine weaponry was supplanted by handheld weapons and forelimbs freed by bipedal locomotion (Carrier, 2011; Darwin, 1871; McHenry, 1991). Clubs, spears, and hurled stones may have obviated biting by keeping enemies at a distance in the way that antlers appear to have replaced large maxillary canines in several deer species (Barrette, 1977). In addition, our shift to habitual bipedalism and its associated orthograde posture enhanced the injuriousness of physical blows (Carrier, 2011).

Male chimpanzees make and use tools, including using branches in dominance displays (but not as offensive weapons; van Lawick-Goodall, 1968), suggesting that tools have been used since the last common ancestor of *Pan* and *Homo*. While the earliest evidence of a weapon-inflicted wound has been dated to roughly 100,000 years ago (Pickering et al., 2000), the emergence of manufactured stone tools by at least 3.4 million years ago (Harmand et al., 2015; McPherron et al., 2010) suggests that handheld weapons were used far earlier. Indeed, it is difficult to imagine an ancestral species with the mental capacity to shape stones for use as cutting tools, and with males fighting over mates, in which males would not also utilize branches, bones, antlers, and other materials in their environment as weapons.

The use of projectile weapons such as hurled rocks and spears may have contributed to the very large male advantage in throwing velocity (3.5 standard deviations by age 12 years; Thomas and French, 1985), as well as men's 1.5 standard deviation advantage in targeting and avoiding projectiles (Watson and Kimura, 1991). This targeting difference remains large after controlling for experience (Watson and Kimura, 1991) and appears to depend developmentally on early androgen exposure (Hines et al.,

2003). Across societies, the manufacture and use of weapons against same-sex rivals is ubiquitous among men and rare among women (Archer, 2004; Ellis et al., 2008; Smith and Smith, 1995; Warner et al., 2005).

The development of handheld weapons represented a watershed moment in hominin evolution, imbuing physical contests among men with a previously unknown degree of lethality. Moreover, for the first time in primate evolution, individuals were able to aggress from a distance, reducing the advantage of anatomical weaponry and possibly spurring the diminution of sexual dimorphism in body, and especially canine, size. This inference has important implications: if the use of handheld weapons is responsible for reduction in the typical trappings of primate intrasexual selection, then an examination of body size dimorphism and canine size dimorphism may lead us to underestimate the intensity of contest competition over the evolution of our species.

Dominance Displays

Traits such as physical aggression, pain tolerance, size, strength, facial robusticity, and weapons use may have served to make men more competitive in physical contests. However, physical violence is costly energetically and in terms of risk of injury or death, as well as risk of retribution (eg, Beckerman et al., 2009; Daly and Wilson, 1988). Across species, male contests frequently involve displays and mutual assessment of formidability, often ending when one rival submits before either is injured (see Smith and Parker, 1976 for a discussion of asymmetric contests). While the costs of submission in terms of reduced social status and mating opportunities may be high, the costs of defeat may be higher. As a result, ancestral men capable of accurately assessing rivals' physical formidability likely obtained a selective advantage (Sell et al., 2009, 2010; Wolff and Puts, 2010). Because male–male aggression is culturally ubiquitous (Daly and Wilson, 1988) and characterizes all extant apes (Puts, 2010), we can be confident that there was selective pressure for such acuity ancestrally.

Men are therefore expected to attend closely to the formidability and volatility of their same-sex competitors, to exercise caution accordingly, and to use nonviolent means such as threats and negotiation to obtain status and valued resources. Men appear to utilize cues such as facial appearance (Carrier and Morgan, 2015; Sell et al., 2014; Sell et al., 2009; Zilioli et al., 2014), muscularity (Hill et al., 2013), and height (Stulp et al., 2015) to assess one another's formidability. However, some traits that influence dominance perceptions may have been shaped by selection specifically to signal formidability, as we now discuss.

Behavioral Displays of Formidability

Men may avoid potentially deadly conflict by displaying their formidability to rivals in diverse ways, including greater risk-taking behavior when peers are present (Ginsburg and Miller, 1982; Morrongiello and Dawber, 2004) and when those peers are male (Ermer et al., 2008). In support of this, research has associated dangerous risk-taking with perceptions of physical formidability (Fessler et al., 2014), suggesting that risk-taking and acuity to risk-taking may have evolved for success in contests.

Among the Yanomamo, contests often involve "shouting matches, chest pounding duels, side slapping duels, club fights, fights with axes and machetes, and shooting with bows and arrows with the intent to kill" (Chagnon, 1988, p. 986). Among the Meriam of Australia, the hunting of large sea turtles is physically demanding, potentially injurious, and may function to signal formidability to other men (Bliege Bird et al., 2001; Smith et al., 2003). Optimal foraging and reciprocal altruism are unlikely to explain turtle hunting behavior. Turtle hunting is inefficient as a means of procuring food, hunters typically give away the meat at feasts, and this altruism tends not to be reciprocated. In addition, women do not report greater attraction to turtle hunters, so turtle hunting does not appear to function in mate attraction either (Smith et al., 2003). However, turtle hunting is respected by men, and turtle hunters report earlier onset of sexual behavior and larger numbers of sex partners than nonhunters, as well as 2.4 times greater lifetime reproductive success, with an even larger difference for hunt leaders (Smith et al., 2003).

Men's greater average interest in playing and observing sports, both in the contemporary United States (Deaner et al., 2012) and across traditional societies (Deaner and Smith, 2013), may also reflect selection for displays of formidability—as well as for physical aggression, interest in competition, and the predisposition to engage in activities that build strength and hone skills useful in contests. The male bias in sports participation is striking: in a sample of 50 societies taken from the Human Relations Area Files, males participated in 95% of all sports, females in only 20%, with men predominating especially in combat-related sports (Deaner and Smith, 2013).

Anatomical Threat Displays

Humans are among the most visually sexually dimorphic primates (Dixson et al., 2005), and recent research suggests that at least some conspicuous traits may function to increase men's appearance of formidability. For example, beards and eyebrow hair grow at puberty in males and may signal formidability through associations with physical maturity and testosterone levels and by increasing the apparent size of the jaw and brow (Guthrie, 1970;

Muscarella and Cunningham, 1996; Neave and Shields, 2008). Male faces with beards are rated as more dominant but not more attractive than the same faces clean-shaven (Dixson and Vasey, 2012; Muscarella and Cunningham, 1996; Neave and Shields, 2008).

Likewise, both correlational (Hodges-Simeon et al., 2010) and experimental (Feinberg et al., 2005; Puts et al., 2006, 2007; Wolff and Puts, 2010) research shows positive relationships between vocal masculinity, such as low pitch and vocal timbre, and perceptions of men's dominance. Men's vocal tracts are 15% longer, and their vocal folds 60% longer, than women's (Fant, 1960; Titze, 2000), several times the 7%–8% expected from the sex difference in stature (Gaulin and Boster, 1985). Elevated testosterone levels at puberty cause males' vocal folds to grow longer and thicker than those of females, both absolutely and relative to overall body growth (Harries et al., 1997; Hollien et al., 1994). Men's larger vocal folds consequently vibrate at a fundamental frequency approximately half that of females during phonation, which we perceive as a lower pitch. Similarly, males' larynges descend a full vertebra lower than females' at puberty (Fitch and Giedd, 1999), producing a longer vocal tract and resulting in lower, more closely spaced formant frequencies and a deeper, richer-sounding timbre.

In a cross-cultural sample of voice recordings, men accurately assessed physical strength from the voice even when listening to unfamiliar languages (Sell et al., 2010). Although pitch and timbre track body size within-sex only modestly (González, 2004; Lass and Brown, 1978; Pisanski et al., 2014; Rendall et al., 2005), masculine voices have also been associated with physical aggressiveness, testosterone levels, and peer evaluations of fighting ability (Hill et al., 2013; Puts et al., 2012a). It may be the case that masculine voices are reliable signals of dominance even while masculine voices are only modestly associated with any particular correlate of dominance.

Dominance, Mating, and Reproductive Success

Displays of formidability, whether behavioral or anatomical, may have contributed to mating success among ancestral men by increasing dominance (coerced social status) and prestige (freely conferred deference; Henrich and Gil-White, 2001). Displays of formidability may influence prestige because dominant men can make strong leaders and powerful allies and may also possess skills worthy of emulation. Indeed, experimental evidence suggests that social status is conferred upon dominant men in proportion to their being viewed as likely to generate benefits for the group via within-group enforcement and between-group representation (Lukaszewski et al., 2015). Both dominance and prestige can thus aid in social competition over all contested resources, including food and territory, as well as mates (West-Eberhard, 1983). Indeed, success in competition with other males has been shown to increase men's preferences for feminine female mates (Welling et al., 2013), suggesting that success in male–male competition increases access to desirable sex partners.

In non-Western samples, both dominance and prestige have been associated with increased mating and reproductive success in men (Chagnon, 1988; Smith et al., 2003; von Rueden et al., 2011). However, this does not imply that sexual selection has favored high levels of unrestrained male belligerence. As noted previously, physical aggression is costly and should be dependent upon context, including the likelihood of defeat and the threat of retribution. For example, among the extremely bellicose Waorani of Ecuador, men who participated in the most raids of other villages did not have more wives or offspring (Beckerman et al., 2009). Although failure to avenge homicides may be perceived as a sign of weakness among the Waorani, raiding also brought immediate retribution against the raider's village. It is thus possible that a moderate level of raiding represented the optimal balance between the costs of retribution and the costs of appearing weak.

Among Western undergraduate students, a component of mating success—number of sex partners in the past year—was positively related to self-rated fighting ability in two samples (Wolff and Puts, 2010), and male acquaintances' ratings of fighting ability, as well as size and muscularity, in another sample (Hill et al., 2013). Displays of physical competitive ability such as sports performance (Faurie et al., 2004; Honekopp et al., 2007) and gang membership (Palmer and Tilley, 1995) have also been positively related to mating success.

In addition, traits that influence perceptions of dominance predict mating and reproductive success. For example, a masculine, dominant-sounding voice has been associated with greater mating success in samples of US undergraduates (Hill et al., 2013; Hodges-Simeon et al., 2011; Puts, 2005), as well as with greater reproductive success in a sample of Tanzanian foragers (Apicella et al., 2007). Likewise, dominant facial appearance has been found to predict eventual military rank and reproductive success among military cadets (Mueller and Mazur, 1997).

Coalitional Aggression

Males are more likely than females to kill and be killed by conspecifics among our closest living relatives, chimpanzees (Wrangham et al., 2006), who, like humans, engage in

coalitional aggression. Wrangham and Glowacki (2012, p. 20) argue that humans generally conform to the pattern seen in chimps: "consistent intergroup hostility, safe killing, and benefits from intergroup dominance." Thus, aggressive behavior among allied groups of males, which presents early via boyhood competition (Geary et al., 2003), has likely not only long been a feature of human life (eg, Bamforth, 1994; Frayer, 1997), but may also be a more primitive feature of our primate heritage. There are, however, important distinctions that set humans apart. Notably, hunter-gatherer groups display an ability for peacemaking involving protracted periods of nonviolence toward rival groups that is uncharacteristic of chimpanzees. As Wrangham (1999, p. 18) writes, "Peace is the normal human condition, in the sense that most human groups, for most of the time, are not at war."

A further difference is that chimpanzees engage in far more overt aggression overall, but human aggression is more often lethal, so that chimps and humans living in subsistence societies exhibit similar levels of lethal aggression (Wrangham et al., 2006). For example, the Arnhem Land people of Australia are characterized by an unusually high rate of physical aggression among human populations (Wrangham et al., 2006) but nevertheless display a rate of physical attack two orders of magnitude below that of chimpanzees. In light of this, a comparison with chimps seems apt only to a point in informing our understanding of the possible evolutionary history of human violence. Perhaps the lethality of human weapons elevates the importance of threats, deference, and peacemaking in relation to physical attacks when negotiating intragroup dominance hierarchies and intergroup conflict.

In addition, the substantial death tolls attributable to violence recorded among traditional human societies occur at a level of social complexity greater than physical contests between two males. Of importance is the presence of "organized and sanctioned group violence that involves armed conflict, including confrontations that combatants recognize may result in deliberate killing," as Webster (1998, pp. 313–314) has defined warfare. Conflicts, according to Webster, are perpetrated "with the intent of maintaining the status quo or bringing about a shift of power relations, usually the latter." This definition is similar to understandings of coalitional violence in chimpanzees, which Wrangham's (1999) imbalance-of-power hypothesis argues is contingent on (1) hostility and (2) power asymmetries among groups. The psychological traits that might be favored in the service of coalitional aggression include, as Wrangham (1999, p. 23) suggests, "a tendency to classify others as in-group or out-group, to regard members of out-groups as potential prey, to be alert to (or search for) power asymmetries between in-group and out-group parties, and to be ruthless in attacking out-group parties when the perceived power asymmetry is sufficiently great."

While there are no doubt myriad proximate motivations for organized group violence in our species, such as a desire for slaves, territory, political control, revenge, resolution of economic disagreements, and more fruitful environments (eg, Keeley, 1996), selection ultimately favors traits that contribute to reproduction. Hence, it is at least parsimonious to hypothesize that reproduction lies at the root of coalitional violence, as well. Even when a desire for resources or political control is the immediate cause, these desires may themselves have been forged in the fires of mating competition.

By way of raiding, men are able to forcibly procure female mates through "bride theft," which appears to be a species-typical behavioral trait (Ayres, 1974). Across 10 traditional Amazonian societies, women were captured during 26% of raids occurring within a language family and 54% of raids occurring across language families (Walker and Bailey, 2013). Intergroup aggression among both chimpanzees (Mitani et al., 2010) and humans (Bollig, 1990; Mathew and Boyd, 2014) may additionally enable males to obtain territory and resources that contribute to their mating success. Among human subsistence societies, men appear well aware of what is in the reproductive balance. As Chagnon (1988) reports of the Yanomamo, a desire for women is the main impetus for engaging in warfare, and, importantly, this is the top reason given by Yanomamo, a finding not unique to that particular society. While reasons for warfare and lesser forms of coalitional violence are undoubtedly complex, the desire for mates is acknowledged as a nearly ubiquitous motivation for preindustrial warfare, even among scholars generally unsympathetic to sociobiological theories of behavioral evolution (eg, Keeley, 1996).

Male coalitional violence, regardless of its most immediate cause, has produced an archaeological record riddled with evidence of violent, often lethal, physical aggression among men stretching back beyond the advent of agriculture (Lahr et al., 2016). In one North American paleoindian burial site, roughly 16% of skeletal remains indicate violent death, 5% showing evidence of having been scalped, and 4% decapitated (Milner et al., 1991). Moreover, males account for a higher percentage of victims of violence among all individuals of known sex. This is far from an aberrant finding, with other burial sites yielding similar results. Andrushko et al. (2005) estimated from a burial site of 59 males and 86 females that at least 20% of males, but only 2% of females, experienced a violent death, likely the result of warfare, as evinced by perimortem amputation. The men, furthermore, tended to be young adults, which is the age range of fiercest competition for mates.

Of course, the relationship between male coalitional violence and reproductive success is not always linear and positive. As noted earlier, among the Waorani of Ecuador, Beckerman et al. (2009) report poorer reproductive success as well as exceptionally high mortality rates among the most ardent warriors. Among humans everywhere, there are great costs associated with aggression (Chagnon, 1988). This may result in a curvilinear relationship between aggression and reproductive success, with a maximum that is likely contingent on numerous aspects of the social environment. There would have thus been great benefit ancestrally associated with correctly assessing the potential costs and likelihood of success in a raid, just as there would have been great benefit in correctly assessing the physical formidability of a single male rival. Just as there would be costs to stealing another man's mate, there are costs to participating in a raid to steal the mates of many men. The costs and benefits associated with intragroup aggression may have selected for high levels of intragroup cooperation specifically in the context of warfare. Indeed, experimental research has shown males to exhibit greater group-level contribution in the face of competition from other groups (Van Vugt et al., 2007).

ALTERNATIVES TO MALE CONTESTS

We have reviewed evidence that men's phenotypes are partly products of ancestral contest competition for mates. Men exhibit each of the traits typical of species with male contests, and these traits appear to have been shaped by sexual selection; they are sexually dimorphic and predict men's mating success as well as success in contest competition. Many of these traits (eg, deep voices, beards, muscularity) also emerge at sexual maturity. The exceptions are behaviors that require years of practice to hone relevant skills: fighting, weapons use, behavioral displays of formidability, and coalition formation (eg, Pellis and Pellis, 2007; Thomas and French, 1985)—all of which exhibit prepubertal sex differences, although the sexes may further diverge at puberty. However, we have not yet considered alternative hypotheses: whether some of the previously mentioned traits were shaped by other selective pressures, or arose as byproducts of selection on developmentally correlated traits.

For example, some human sexual dimorphisms may partly be products of a sexual division of labor that is essentially ubiquitous across forager societies: men spend more time hunting, especially larger game, and women spend more time gathering or hunting smaller game (Murdock, 1967). Thus, ecological selection may have contributed to men's greater size, strength, and weapons proficiency to the extent that these contributed to hunting success ancestrally (Kaplan et al., 2000). However, other of men's traits, such as beards, deep voices, more robust faces, and high levels of same-sex aggression, are not easily understood as adaptations for hunting. In addition, given that male contests and sexual size dimorphism probably characterized the common ancestor of the great apes, contest competition likely predates specialized hunting and the human sexual division of labor by several million years. Hence, it is more likely that the sexual division of labor is partly a consequence rather than the initial cause of these anatomical dimorphisms, although hunting likely imposed additional selection pressures on these male traits.

Some aspects of men's phenotypes may also have been produced via female choice, or through a combination of contests and female choice. Because traits that evolve in contest competition are often costly to produce and maintain and are constantly tested by competitors, such traits may represent honest indicators of heritable fitness, and females may consequently evolve preferences for them (Berglund et al., 1996). On the one hand, masculine bodies, faces, and voices in men have indeed been found to increase attractiveness to women (Frederick and Haselton, 2007; Puts et al., 2012b). On the other hand, the influence of facial and vocal masculinity on ratings of dominance is considerably larger and more consistently positive than the effects on attractiveness (Puts et al., 2012b). Recent work suggests that male facial masculinity may not be universally preferred by women across human societies, whereas it much more consistently conveys the impression of aggressiveness (Scott et al., 2014). Likewise, beards reliably increase perceptions of age, aggression, dominance, and social status across societies, but generally decrease attractiveness to women (Dixson and Vasey, 2012; Muscarella and Cunningham, 1996; Neave and Shields, 2008). Furthermore, in samples spanning Western (Hill et al., 2013), traditional agricultural (Llaurens et al., 2009), and preindustrial (Smith et al., 2003) societies, men's mating success has been found to relate more strongly to dominance among men and the traits that contribute to dominance than to attractiveness to women. Across the suite of male secondary sexual characteristics, then, selection for success in physical contests may have been either attenuated or augmented by selection for attractiveness to females. In general, however, men's traits function far more effectively in the context of male contests than in mate attraction, and thus they do not appear to have evolved primarily as sexual ornaments to attract women.

Another possibility is that some of men's traits represent developmental byproducts of male body size or testosterone levels. Strength increases with body mass and height (Balogun et al., 1991), for example, although other male traits are not known to relate to body size (eg, beards) or relate only weakly (eg, voice pitch; Pisanski et al., 2014). However, even traits that are correlated with size are far more sexually dimorphic than would be predicted from sex differences in size alone (Puts et al., 2012b). Similarly,

androgens such as testosterone play important roles in the development of male-typical traits, so one might conjecture that these traits are merely developmental side-effects of androgens. This viewpoint confuses proximate and ultimate explanation, leaving unresolved the question of why humans have evolved to respond to testosterone by growing facial hair and longer-thicker vocal folds, for example. Why instead do we not respond to testosterone by growing antlers, as in red deer (Suttie et al., 1995), or canines, as in many other primates (Van Wagenen and Hurme, 1950)? Why does testosterone not increase paternal investment, as in the California mouse (*Peromyscus californicus*) (Gleason and Marler, 2013), rather than having the opposite effect, as it does in many vertebrates, apparently including humans (Kuzawa et al., 2009; Puts et al., 2015b)? Clearly, different species, even closely related ones, can evolve quite different responses to the same hormones. An evolutionary history of male contests parsimoniously explains why, in humans, a particular constellation of sexually dimorphic traits including large size may be developmentally linked to testosterone and to each other.

A final alternative to contest competition in our hominin ancestors is phylogenetic inertia—the idea that we have inherited our traits from ancestral species rather than experiencing selection for these traits in our own species. Fossil and comparative evidence indicate that we did indeed inherit traits such as greater male size and aggression from an ancient hominin ancestor. However, for other traits such as deep voices (Puts et al., 2016), beards, and the use of handheld weapons, this appears not to have been the case. Even for traits such as greater male size and aggression that were likely sexually dimorphic in our common ancestor with chimpanzees, we would expect considerable reduction in modern humans if these traits were not functional over recent hominin evolution, given their substantial costs. And yet, as discussed earlier, men's physical aggression is equally lethal to that of male chimpanzees, and we are more sexually dimorphic than chimpanzees in both skeletal size and fat-free mass.

Despite the comparatively strong overall evidence for the importance of contest competition over men's evolution, each of these alternative factors may have played a role. These are not mutually exclusive alternatives; any aspect of the phenotype can experience multiple selection pressures, as well as responding to selection on other traits with which it is developmentally correlated.

CONCLUSION

We have reviewed multiple converging lines of evidence supporting a role for contest competition in shaping the human male phenotype. Sex differences in parental investment, reproductive rates, and reproductive variance; the OSR; and patterns of mating and marriage—all indicate a history of moderately strong sexual selection among our male ancestors.

Contest competition in particular tends to favor size, strength, aggression, weapons, and threat displays, and men display all of these features. Traits that point to an evolutionary past in which our male ancestors competed for mates through force and threat include a proclivity for same-sex violence including coalitional aggression, higher pain threshold and tolerance compared to women, increased body size and strength, facial robusticity, fashioning and use of weapons, beards, deep voices, and behavioral displays of formidability. This evidence is taken from research across fields ranging from human anatomy and physiology to psychology, ethnography, paleoanthropology, animal behavior, and archaeology. The alternative hypotheses that men's traits were shaped by selection for hunting ability, female mate choice, or selection operating on developmentally correlated traits—or that men's traits are consequences of phylogenetic inertia—can help account for some of the above aspects of men's phenotypes, but not others. The success of any hypothesis is contingent on a parsimonious explanation of the totality of evidence, and only contest competition accomplishes this. In some ways, we may be more gorilla-like, or chimp-like, than we prefer to suppose.

It is important to bear in mind, however, that while human nature includes a propensity for violence in both individual and coalitional forms, we are also capable of negotiation, compromise, and restraint. For a species currently numbering in the billions that now possesses weapons capable of bringing about its own annihilation, the importance of understanding our capacity for violence is more than academic—it can potentially illuminate and suggest solutions to problems of pressing societal concern.

REFERENCES

Abe, T., Kearns, C., Fukunaga, T., 2003. Sex differences in whole body skeletal muscle mass measured by magnetic resonance imaging and its distribution in young Japanese adults. British Journal of Sports Medicine 37 (5), 436–440.

Andersson, M., 1982. Female choice selects for extreme tail length in a widowbird. Nature 299 (5886), 818–820.

Andersson, M.B., 1994. Sexual Selection. Princeton University Press.

Andrushko, V.A., Latham, K.A., Grady, D.L., Pastron, A.G., Walker, P.L., 2005. Bioarchaeological evidence for trophy-taking in prehistoric central California. American Journal of Physical Anthropology 127 (4), 375–384. http://dx.doi.org/10.1002/ajpa.20044.

Antón, S.C., 2003. Natural history of Homo erectus. American Journal of Physical Anthropology 122 (S37), 126–170.

Apicella, C.L., Feinberg, D.R., Marlowe, F.W., 2007. Voice pitch predicts reproductive success in male hunter-gatherers. Biology Letters 3 (6), 682–684. http://dx.doi.org/10.1098/rsbl.2007.0410.

Apostolou, M., 2007. Sexual selection under parental choice: the role of parents in the evolution of human mating. Evolution and Human

Behavior 28 (6), 403–409. http://dx.doi.org/10.1016/j.evolhumbehav.2007.05.007.

Archer, J., 2004. Sex differences in aggression in real-world settings: a meta-analytic review. Review of General Psychology 8 (4), 291.

Archer, J., 2009. Does sexual selection explain human sex differences in aggression? Behavioral and Brain Sciences 32 (3–4), 249–266. http://dx.doi.org/10.1017/S0140525X09990951 discussion 266–311.

Ayres, B., 1974. Bride theft and raiding for wives in cross-cultural perspective. Anthropological Quarterly 238–252.

Balogun, J.A., Akinloye, A.A., Adenlola, S.A., 1991. Grip strength as a function of age, height, body weight and Quetelet index. Physiotherapy Theory and Practice 7 (2), 111–119.

Bamforth, D.B., 1994. Indigenous people, indigenous violence: precontact warfare on the North American Great Plains. Man 95–115.

Barrette, C., 1977. Fighting behavior of muntjac and the evolution of antlers. Evolution 169–176.

Bateman, A.J., 1948. Intra-sexual selection in Drosophila. Heredity 2 (Pt 3), 349–368.

Beckerman, S., Erickson, P.I., Yost, J., Regalado, J., Jaramillo, L., Sparks, C., Long, K., 2009. Life histories, blood revenge, and reproductive success among the Waorani of Ecuador. Proceedings of the National Academy of Sciences of the United States of America 106 (20), 8134–8139. http://dx.doi.org/10.1073/pnas.0901431106 pii:0901431106.

Berglund, A., Bisazza, A., Pilastro, A., 1996. Armaments and ornaments: an evolutionary explanation of traits of dual utility. Biological Journal of the Linnean Society 58 (4), 385–399.

Berry, J.F., Shine, R., 1980. Sexual size dimorphism and sexual selection in turtles (Order Testudines). Oecologia 44 (2), 185–191.

Bliege Bird, R., Smith, E., Bird, D., 2001. The hunting handicap: costly signaling in human foraging strategies. Behavioral Ecology and Sociobiology 50 (1), 9–19. http://dx.doi.org/10.1007/s002650100338.

Blurton Jones, N., 1987. Bushman birth spacing: direct tests of some simple predictions. Ethology and Sociobiology 8 (3), 183–203.

Bollig, M., 1990. Ethnic conflicts in North-west Kenya: Pokot-Turkana raiding 1969 1984. Zeitschrift für Ethnologie 73–90.

Borgerhoff Mulder, M., 2009. Serial monogamy as polygyny or polyandry?: marriage in the tanzanian pimbwe. Human Nature 20 (2), 130–150. http://dx.doi.org/10.1007/s12110-009-9060-x.

Brink, O., Vesterby, A., Jensen, J., 1998. Pattern of injuries due to interpersonal violence. Injury 29 (9), 705–709.

Brown, G.R., Laland, K.N., Mulder, M.B., 2009. Bateman's principles and human sex roles. Trends in Ecology and Evolution 24 (6), 297–304. http://dx.doi.org/10.1016/j.tree.2009.02.005.

Brunet, M., Guy, F., Pilbeam, D., Mackaye, H.T., Likius, A., Ahounta, D., Boisserie, J.-R., 2002. A new hominid from the upper Miocene of Chad, Central Africa. Nature 418 (6894), 145–151.

Buckle, L., Gallup, G.G., Rodd, Z.A., 1996. Marriage as a reproductive contract: patterns of marriage, divorce, and remarriage. Ethology and Sociobiology 17 (6), 363–377.

Campbell, A., 2013. The evolutionary psychology of women's aggression. Philosophical Transactions of the Royal Society B: Biological Sciences 368 (1631), 20130078.

Carrier, D.R., Morgan, M.H., 2015. Protective buttressing of the hominin face. Biological Reviews of the Cambridge Philosophical Society 90 (1), 330–346. http://dx.doi.org/10.1111/brv.12112.

Carrier, D.R., 2011. The advantage of standing up to fight and the evolution of habitual bipedalism in hominins. PLoS One 6 (5), e19630.

Chagnon, N.A., 1988. Life histories, blood revenge, and warfare in a tribal population. Science 239 (4843), 985–992.

Chagnon, N., 1992. Yanomamo, fourth ed. Harcourt, Brace, Jovanovich, Fort Worth, Texas.

Clutton-Brock, T., Harvey, P.H., 1984. Comparative approaches to investigating adaptation. Behavioural ecology. An Evolutionary Approach 7–29.

Clutton-Brock, T.H., Vincent, A.C., 1991. Sexual selection and the potential reproductive rates of males and females. Nature 351 (6321), 58–60.

Conniff, R., 2009. Discovering gorilla. Evolutionary Anthropology: Issues, News, and Reviews 18 (2), 55–61. http://dx.doi.org/10.1002/evan.20203.

Daly, M., Wilson, M., 1988. Homicide. Transaction Publishers.

Daly, M., Wilson, M., 1990. Killing the competition. Human Nature 1 (1), 81–107.

Darwin, C., 1871. The Descent of Man and Selection in Relation to Sex. Murray, London.

Deaner, R.O., Smith, B.A., 2013. Sex differences in sports across 50 societies. Cross-Cultural Research 47 (3), 268–309. http://dx.doi.org/10.1177/1069397112463687.

Deaner, R.O., Geary, D.C., Puts, D.A., Ham, S.A., Kruger, J., Fles, E., Grandis, T., 2012. A sex difference in the predisposition for physical competition: males play sports much more than females even in the contemporary U.S. PLoS One 7 (11), e49168. http://dx.doi.org/10.1371/journal.pone.0049168PONE-D-12-18846.

Dixson, B.J., Vasey, P.L., 2012. Beards augment perceptions of men's age, social status, and aggressiveness, but not attractiveness. Behavioral Ecology 23 (3), 481–490. http://dx.doi.org/10.1093/beheco/arr214.

Dixson, A., Dixson, B., Anderson, M., 2005. Sexual selection and the evolution of visually conspicuous sexually dimorphic traits in male monkeys, apes, and human beings. Annual Review of Sex Research 16 (1), 1–19.

Eibl-Eibesfeldt, I., 1989. Human Ethology (Transl. by P. Wiessner-Larsen and A. Henneman). Aldine de Gruyter, New York.

Ellis, L., Hershberger, S., Field, E., Wersinger, S., Pellis, S., Geary, D., Karadi, K., 2008. Sex Differerences: Summarizing More than a Century of Scientific Research. Psychology Press, New York.

Emlen, S.T., Oring, L.W., 1977. Ecology, sexual selection, and the evolution of mating systems. Science 197 (4300), 215–223.

Ermer, E., Cosmides, L., Tooby, J., 2008. Relative status regulates risky decision making about resources in men: evidence for the co-evolution of motivation and cognition. Evolution and Human Behavior 29 (2), 106–118.

Fant, G., 1960. Acoustic Theory of Speech Production. The Hague, Mouton.

Faurie, C., Pontier, D., Raymond, M., 2004. Student athletes claim to have more sexual partners than other students. Evolution and Human Behavior 25 (1), 1–8.

Feinberg, D.R., Jones, B.C., Little, A.C., Burt, D.M., Perrett, D.I., 2005. Manipulations of fundamental and formant frequencies influence the attractiveness of human male voices. Animal Behaviour 69 (3), 561–568. http://dx.doi.org/10.1016/j.anbehav.2004.06.012.

Fessler, D.M.T., Tiokhin, L.B., Holbrook, C., Gervais, M.M., Snyder, J.K., 2014. Foundations of the Crazy Bastard Hypothesis: nonviolent physical risk-taking enhances conceptualized formidability. Evolution and Human Behavior 35 (1), 26–33. http://dx.doi.org/10.1016/j.evolhumbehav.2013.09.003.

Fillingim, R.B., King, C.D., Ribeiro-Dasilva, M.C., Rahim-Williams, B., Riley, J.L., 2009. Sex, gender, and pain: a review of recent clinical and experimental findings. The Journal of Pain 10 (5), 447–485.

Fitch, W.T., Giedd, J., 1999. Morphology and development of the human vocal tract: a study using magnetic resonance imaging. The Journal of the Acoustical Society of America 106 (3), 1511–1522.

Fossey, D., 1983. Gorillas in the Mist. Houghton Mifflin, Boston.

Frayer, D.W., 1997. Ofnet: evidence for a Mesolithic massacre. In: Troubled Times: Violence and Warfare in the Past, vol. 3, pp. 181–216.

Frederick, D.A., Haselton, M.G., 2007. Why is muscularity sexy? Tests of the fitness indicator hypothesis. Personality and Social Psychology Bulletin 33 (8), 1167–1183.

Frederick, D.A., Jenkins, B.N., 2015. Height and body mass on the mating market associations with number of sex partners and extra-pair sex among heterosexual men and women aged 18–65. Evolutionary Psychology 13 (3), 1474704915604563.

Gangestad, S.W., Thornhill, R., 2008. Human oestrus. Proceedings of the Royal Society B: Biological Sciences 275 (1638), 991–1000. http://dx.doi.org/10.1098/rspb.2007.1425.

Gaulin, S., Boster, J., 1985. Cross-cultural differences in sexual dimorphism: is there any variance to be explained? Ethology and Sociobiology 6 (4), 219–225.

Geary, D.C., Byrd-Craven, J., Hoard, M.K., Vigil, J., Numtee, C., 2003. Evolution and development of boys' social behavior. Developmental Review 23 (4), 444–470.

Geary, D.C., 2000. Evolution and proximate expression of human paternal investment. Psychological Bulletin 126 (1), 55–77. http://dx.doi.org/10.1037//0033-2909.126.1.55.

Ginsburg, H.J., Miller, S.M., 1982. Sex differences in children's risk-taking behavior. Child Development 426–428.

Gleason, E.D., Marler, C.A., 2013. Non-genomic transmission of paternal behaviour between fathers and sons in the monogamous and biparental California mouse. Proceedings of the Royal Society of London B: Biological Sciences 280 (1763), 20130824.

Glenday, C., 2013. Guinness World Records 2013. Random House LLC.

González, J., 2004. Formant frequencies and body size of speaker: a weak relationship in adult humans. Journal of Phonetics 32 (2), 277–287. http://dx.doi.org/10.1016/s0095-4470(03)00049-4.

Gordon, A.D., Green, D.J., Richmond, B.G., 2008. Strong postcranial size dimorphism in Australopithecus afarensis: results from two new resampling methods for multivariate data sets with missing data. American Journal of Physical Anthropology 135 (3), 311–328. http://dx.doi.org/10.1002/ajpa.20745.

Guthrie, R., 1970. Evolution of human threat display organs. Evolutionary Biology 4, 257–302.

Hanno, 1832. The Voyage of Hanno, commander of the Carthaginians, round the parts of Lilxya beyond the Pillars of Hercules, which he deposited in the temple of Saturn (Anonymus, Trans.). In: Heeren, A.H.L. (Ed.), Historical Researches into the Politics, Intercourse and Trade of the Cathaginians, Ethiopians, and Egyptians. D.A. Talboys, Oxford, pp. 492–501.

Harcourt-Smith, W.E., 2007. 5 The Origins of Bipedal Locomotion Handbook of Paleoanthropology. Springer, pp. 1483–1518.

Harmand, S., Lewis, J.E., Feibel, C.S., Lepre, C.J., Prat, S., Lenoble, A., Roche, H., 2015. 3.3-million-year-old stone tools from Lomekwi 3, West Turkana, Kenya. Nature 521 (7552), 310–315. http://dx.doi.org/10.1038/nature14464. http://www.nature.com/nature/journal/v521/n7552/abs/nature14464.html#supplementary-information.

Harries, M., Walker, J.M., Williams, D.M., Hawkins, S., Hughes, I., 1997. Changes in the male voice at puberty. Archives of Disease in Childhood 77 (5), 445–447.

Henrich, J., Gil-White, F.J., 2001. The evolution of prestige: freely conferred deference as a mechanism for enhancing the benefits of cultural transmission. Evolution and Human Behavior 22 (3), 165–196.

Hill, K.R., Hurtado, A.M., 1996. Ache Life History: The Ecology and Demography of a Foraging People. Transaction Publishers.

Hill, A.K., Hunt, J., Welling, L.L.M., Cárdenas, R.A., Rotella, M.A., Wheatley, J.R., Puts, D.A., 2013. Quantifying the strength and form of sexual selection on men's traits. Evolution and Human Behavior 34 (5), 334–341. http://dx.doi.org/10.1016/j.evolhumbehav.2013.05.004.

Hines, M., Fane, B.A., Pasterski, V., Mathews, G., Conway, G., Brook, C., 2003. Spatial abilities following prenatal androgen abnormality: targeting and mental rotations performance in individuals with congenital adrenal hyperplasia. Psychoneuroendocrinology 28 (8), 1010–1026.

Hodges-Simeon, C.R., Gaulin, S.J., Puts, D.A., 2010. Different vocal parameters predict perceptions of dominance and attractiveness. Human Nature 21 (4), 406–427. http://dx.doi.org/10.1007/s12110-010-9101-5.

Hodges-Simeon, C.R., Gaulin, S.J., Puts, D.A., 2011. Voice correlates of mating success in men: examining "contests" versus "mate choice" modes of sexual selection. Archives of Sexual Behavior 40 (3), 551–557. http://dx.doi.org/10.1007/s10508-010-9625-0.

Hollien, H., Green, R., Massey, K., 1994. Longitudinal research on adolescent voice change in males. The Journal of the Acoustical Society of America 96 (5), 2646–2654.

Honekopp, J., Rudolph, U., Beier, L., Liebert, A., Muller, C., 2007. Physical attractiveness of face and body as indicators of physical fitness in men. Evolution and Human Behavior 28 (2), 106–111. http://dx.doi.org/10.1016/j.evolhumbehav.2006.09.001.

Hooper, P.L., Miller, G.F., 2008. Mutual mate choice can drive costly signaling even under perfect monogamy. Adaptive Behavior 16 (1), 53–70.

Hughes, S.M., Gallup, G.G., 2003. Sex differences in morphological predictors of sexual behavior. Evolution and Human Behavior 24 (3), 173–178. http://dx.doi.org/10.1016/s1090-5138(02)00149-6.

Jokela, M., Rotkirch, A., Rickard, I.J., Pettay, J., Lummaa, V., 2010. Serial monogamy increases reproductive success in men but not in women. Behavioral Ecology 21 (5), 906–912. http://dx.doi.org/10.1093/beheco/arq078.

Kaplan, H., Hill, K., Lancaster, J., Hurtado, A.M., 2000. A theory of human life history evolution: diet, intelligence, and longevity. Evolutionary Anthropology: Issues, News, and Reviews 9 (4), 156–185.

Keeley, L.H., 1996. War Before Civilization. Oxford University Press.

Kokko, H., Jennions, M.D., 2008. Parental investment, sexual selection and sex ratios. Journal of Evolutionary Biology 21 (4), 919–948. http://dx.doi.org/10.1111/j.1420-9101.2008.01540.x.

Kokko, H., Klug, H., Jennions, M.D., 2012. Unifying cornerstones of sexual selection: operational sex ratio, Bateman gradient and the scope for competitive investment. Ecology Letters 15 (11), 1340–1351. http://dx.doi.org/10.1111/j.1461-0248.2012.01859.x.

Kuzawa, C.W., Gettler, L.T., Muller, M.N., McDade, T.W., Feranil, A.B., 2009. Fatherhood, pairbonding and testosterone in the Philippines. Hormones and Behavior 56 (4), 429–435.

Lahr, M.M., Rivera, F., Power, R.K., Mounier, A., Copsey, B., Crivellaro, F., Foley, R.A., 2016. Inter-group violence among early Holocene hunter-gatherers of West Turkana, Kenya. Nature 529 (7586), 394–398.

http://dx.doi.org/10.1038/nature16477. http://www.nature.com/nature/journal/v529/n7586/abs/nature16477.html#supplementary-information.

Lande, R., 1980. Sexual dimorphism, sexual selection, and adaptation in polygenic characters. Evolution 292–305.

Lass, N.J., Brown, W.S., 1978. Correlational study of speakers' heights, weights, body surface areas, and speaking fundamental frequencies. The Journal of the Acoustical Society of America 63 (4), 1218–1220.

Lassek, W.D., Gaulin, S.J.C., 2009. Costs and benefits of fat-free muscle mass in men: relationship to mating success, dietary requirements, and native immunity. Evolution and Human Behavior 30 (5), 322–328. http://dx.doi.org/10.1016/j.evolhumbehav.2009.04.002.

Lindenfors, P., Fröberg, L., Nunn, C.L., 2004. Females drive primate social evolution. Proceedings of the Royal Society of London B: Biological Sciences 271 (Suppl. 3), S101–S103.

Llaurens, V., Raymond, M., Faurie, C., 2009. Ritual fights and male reproductive success in a human population. Journal of Evolutionary Biology 22 (9), 1854–1859. http://dx.doi.org/10.1111/j.1420-9101.2009.01793.x.

Lockwood, C.A., Richmond, B.G., Jungers, W.L., Kimbel, W.H., 1996. Randomization procedures and sexual dimorphism inAustralopithecus afarensis. Journal of Human Evolution 31 (6), 537–548.

Lukaszewski, A.W., Simmons, Z.L., Anderson, C., Roney, J.R., 2015. The role of physical formidability in human social status allocation. Journal of Personality and Social Psychology. http://dx.doi.org/10.1037/pspi0000042.

Lynn, B., 1984. Cutaneous nociceptors. In: Holden, A.V., Winlow, W. (Eds.), The Neurobiology of Pain. Manchester UP, Manchester, pp. 97–107.

Maple, T.L., Hoff, M.P., 1982. Gorilla Behavior. Van Nostrand Reinhold Company, New York.

Marlowe, F.W., Berbesque, J.C., 2012. The human operational sex ratio: effects of marriage, concealed ovulation, and menopause on mate competition. Journal of Human Evolution 63 (6), 834–842. http://dx.doi.org/10.1016/j.jhevol.2012.09.004 pii:S0047-2484(12)00163-7.

Marlowe, F.W., 2004. Mate preferences among Hadza hunter-gatherers. Human Nature 15 (4), 365–376.

Mathew, S., Boyd, R., 2014. The cost of cowardice: punitive sentiments towards free riders in Turkana raids. Evolution and Human Behavior 35 (1), 58–64.

McHenry, H.M., 1991. Sexual dimorphism in Australopithecus afarensis. Journal of Human Evolution 20 (1), 21–32.

McPherron, S.P., Alemseged, Z., Marean, C.W., Wynn, J.G., Reed, D., Geraads, D., Bearat, H.A., 2010. Evidence for stone-tool-assisted consumption of animal tissues before 3.39 million years ago at Dikika, Ethiopia. Nature 466 (7308), 857–860. http://www.nature.com/nature/journal/v466/n7308/abs/nature09248.html#supplementary-information.

Milner, G.R., Anderson, E., Smith, V.G., 1991. Warfare in late prehistoric west-central Illinois. American Antiquity 581–603.

Mitani, J.C., Gros-Louis, J., Richards, A.F., 1996. Sexual dimorphism, the operational sex ratio, and the intensity of male competition in polygynous primates. American Naturalist 966–980.

Mitani, J.C., Watts, D.P., Amsler, S.J., 2010. Lethal intergroup aggression leads to territorial expansion in wild chimpanzees. Current Biology 20 (12), R507–R508. http://dx.doi.org/10.1016/j.cub.2010.04.021 pii:S0960-9822(10)00459-8.

Morrongiello, B.A., Dawber, T., 2004. Identifying factors that relate to children's risk-taking decisions. Canadian Journal of Behavioural Science 36 (4), 255.

Mueller, U., Mazur, A., 2001. Evidence of unconstrained directional selection for male tallness. Behavioral Ecology and Sociobiology 50 (4), 302–311. http://dx.doi.org/10.1007/s002650100370.

Mueller, U., Mazur, A., 1997. Facial dominance in *Homo sapiens* as honest signaling of male quality. Behavioral Ecology 8 (5), 569–579.

Murdock, G.P., 1967. Ethnographic Atlas.

Muscarella, F., Cunningham, M.R., 1996. The evolutionary significance and social perception of male pattern baldness and facial hair. Ethology and Sociobiology 17 (2), 99–117.

Neave, N., Shields, K., 2008. The effects of facial hair manipulation on female perceptions of attractiveness, masculinity, and dominance in male faces. Personality and Individual Differences 45 (5), 373–377. http://dx.doi.org/10.1016/j.paid.2008.05.007.

Palmer, C.T., Tilley, C.F., 1995. Sexual access to females as a motivation for joining gangs: an evolutionary approach. The Journal of Sex Research 32 (3), 213–217.

Pawlowski, B., Dunbar, R., Lipowicz, A., 2000. Evolutionary fitness: tall men have more reproductive success. Nature 403 (6766), 156.

Pellis, S.M., Pellis, V.C., 2007. Rough-and-tumble play and the development of the social brain. Current Directions in Psychological Science 16 (2), 95–98.

Pickering, T.R., White, T.D., Toth, N., 2000. Brief communication: cutmarks on a Plio-Pleistocene hominid from Sterkfontein, South Africa. American Journal of Physical Anthropology 111 (4), 579–584.

Pisanski, K., Fraccaro, P.J., Tigue, C.C., O'Connor, J.J., Röder, S., Andrews, P.W., Feinberg, D.R., 2014. Vocal indicators of body size in men and women: a meta-analysis. Animal Behaviour 95, 89–99.

Plavcan, J.M., 2012. Sexual size dimorphism, canine dimorphism, and male-male competition in primates: where do humans fit in? Human Nature 23 (1), 45–67. http://dx.doi.org/10.1007/s12110-012-9130-3.

Puts, D.A., Gaulin, S.J.C., Verdolini, K., 2006. Dominance and the evolution of sexual dimorphism in human voice pitch. Evolution and Human Behavior 27 (4), 283–296. http://dx.doi.org/10.1016/j.evolhumbehav.2005.11.003.

Puts, D.A., Hodges, C.R., Cárdenas, R.A., Gaulin, S.J.C., 2007. Men's voices as dominance signals: vocal fundamental and formant frequencies influence dominance attributions among men. Evolution and Human Behavior 28 (5), 340–344. http://dx.doi.org/10.1016/j.evolhumbehav.2007.05.002.

Puts, D.A., Apicella, C.L., Cardenas, R.A., 2012a. Masculine voices signal men's threat potential in forager and industrial societies. Proceedings of the Royal Society B: Biological Sciences 279 (1728), 601–609. http://dx.doi.org/10.1098/rspb.2011.0829.

Puts, D.A., Jones, B.C., DeBruine, L.M., 2012b. Sexual selection on human faces and voices. The Journal of Sex Research 49 (2–3), 227–243. http://dx.doi.org/10.1080/00224499.2012.658924.

Puts, D.A., Bailey, D.H., Cárdenas, R.A., Burriss, R.P., Welling, L.L., Wheatley, J.R., Dawood, K., 2013. Women's attractiveness changes with estradiol and progesterone across the ovulatory cycle. Hormones and Behavior 63 (1), 13–19. http://dx.doi.org/10.1016/j.yhbeh.2012.11.007 pii:S0018-506X(12)00279-6.

Puts, D.A., Bailey, D.H., Reno, P.L., 2015a. Contest competition in men. In: Buss, D.M. (Ed.), The Handbook of Evolutionary Psychology, second ed., vol. 1. Wiley & Sons.

Puts, D.A., Pope, L.E., Hill, A.K., Cardenas, R.A., Welling, L.L., Wheatley, J.R., Marc Breedlove, S., 2015b. Fulfilling desire: evidence for negative feedback between men's testosterone, sociosexual

psychology, and sexual partner number. Hormones and Behavior 70, 14–21. http://dx.doi.org/10.1016/j.yhbeh.2015.01.006 pii:S0018-506X(15)00014-8.

Puts, D.A., Hill, A.K., Bailey, D.H., Walker, R.S., Rendall, D., Wheatley, J.R., Welling, L.L.M., Dawood, K., Cárdenas, R., Burriss, R.P., Jablonski, N.G., Shriver, M.D., Weiss, D., Lameira, A.R., Apicella, C.L., Owren, M.J., Barelli, C., Glenn, M.E., Ramos-Fernandez, G., 2016. Sexual selection on male vocal fundamental frequency in humans and other anthropoids. Proceedings of the Royal Society B: Biological Sciences 283 (1829), 20152830.

Puts, D.A., 2005. Mating context and menstrual phase affect women's preferences for male voice pitch. Evolution and Human Behavior 26 (5), 388–397. http://dx.doi.org/10.1016/j.evolhumbehav.2005.03.001.

Puts, D.A., 2010. Beauty and the beast: mechanisms of sexual selection in humans. Evolution and Human Behavior 31 (3), 157–175. http://dx.doi.org/10.1016/j.evolhumbehav.2010.02.005.

Puts, D., 2016. Human sexual selection. Current Opinion in Psychology 7, 28–32.

Rendall, D., Kollias, S., Ney, C., Lloyd, P., 2005. Pitch (F_0) and formant profiles of human vowels and vowel-like baboon grunts: the role of vocalizer body size and voice-acoustic allometry. The Journal of the Acoustical Society of America 117 (2), 944. http://dx.doi.org/10.1121/1.1848011.

Reno, P.L., Lovejoy, C.O., 2015. From Lucy to Kadanuumuu: balanced analyses of Australopithecus afarensis assemblages confirm only moderate skeletal dimorphism. PeerJ 3, e925. http://dx.doi.org/10.7717/peerj.925.

Reno, P.L., Meindl, R.S., McCollum, M.A., Lovejoy, C.O., 2003. Sexual dimorphism in Australopithecus afarensis was similar to that of modern humans. Proceedings of the National Academy of Sciences of the United States of America 100 (16), 9404–9409.

Reno, P.L., McCollum, M.A., Meindl, R.S., Lovejoy, C.O., 2010. An enlarged postcranial sample confirms Australopithecus afarensis dimorphism was similar to modern humans. Philosophical Transactions of the Royal Society of London B Biological Sciences 365 (1556), 3355–3363. http://dx.doi.org/10.1098/rstb.2010.0086.

Rhodes, G., Simmons, L.W., Peters, M., 2005. Attractiveness and sexual behavior: does attractiveness enhance mating success? Evolution and Human Behavior 26 (2), 186–201. http://dx.doi.org/10.1016/j.evolhumbehav.2004.08.014.

Riley III, J.L., Robinson, M.E., Wise, E.A., Myers, C.D., Fillingim, R.B., 1998. Sex differences in the perception of noxious experimental stimuli: a meta-analysis. Pain 74 (2), 181–187.

Salzano, F.M., Neel, J.V., Maybury-Lewis, D., 1967. I. Demographic data on two additional villages: genetic structure of the tribe. American Journal of Human Genetics 19 (4), 463.

Schreier, A.L., Swedell, L., 2009. The fourth level of social structure in a multi-level society: ecological and social functions of clans in hamadryas baboons. American Journal of Primatology 71 (11), 948–955.

Schwagmeyer, P., Woontner, S., 1986. Scramble competition polygyny in thirteen-lined ground squirrels: the relative contributions of overt conflict and competitive mate searching. Behavioral Ecology and Sociobiology 19 (5), 359–364.

Scott, I.M., Clark, A.P., Boothroyd, L.G., Penton-Voak, I.S., 2012. Do men's faces really signal heritable immunocompetence? Behavioral Ecology 24, 579–589 ars092.

Scott, I.M., Clark, A.P., Josephson, S.C., Boyette, A.H., Cuthill, I.C., Fried, R.L., Penton-Voak, I.S., 2014. Human preferences for sexually dimorphic faces may be evolutionarily novel. Proceedings of the National Academy of Sciences of the United States of America 111 (40), 14388–14393. http://dx.doi.org/10.1073/pnas.1409643111 pii:1409643111.

Sell, A., Cosmides, L., Tooby, J., Sznycer, D., von Rueden, C., Gurven, M., 2009. Human adaptations for the visual assessment of strength and fighting ability from the body and face. Proceedings of the Royal Society B: Biological Sciences 276 (1656), 575–584. http://dx.doi.org/10.1098/rspb.2008.1177.

Sell, A., Bryant, G.A., Cosmides, L., Tooby, J., Sznycer, D., von Rueden, C., Gurven, M., 2010. Adaptations in humans for assessing physical strength from the voice. Proceedings of the Royal Society B: Biological Sciences 277 (1699), 3509–3518. http://dx.doi.org/10.1098/rspb.2010.0769.

Sell, A., Cosmides, L., Tooby, J., 2014. The human anger face evolved to enhance cues of strength. Evolution and Human Behavior 35 (5), 425–429. http://dx.doi.org/10.1016/j.evolhumbehav.2014.05.008.

Shepherd, J.P., Gayford, J.J., Leslie, I.J., Scully, C., 1988. Female victims of assault: a study of hospital attenders. Journal of Cranio-Maxillofacial Surgery 16, 233–237.

Smith, J.M., Parker, G.A., 1976. The logic of asymmetric contests. Animal Behaviour 24 (1), 159–175.

Smith, T.W., Smith, R.J., 1995. Changes in firearms ownership among women, 1980-1994. Journal of Criminal Law and Criminology 86, 133.

Smith, E.A., Bird, R.B., Bird, D.W., 2003. The benefits of costly signaling: Meriam turtle hunters. Behavioral Ecology 14 (1), 116–126. http://dx.doi.org/10.1093/beheco/14.1.116.

Sternberg, W.F., Bokat, C., Kass, L., Alboyadjian, A., Gracely, R.H., 2001. Sex-dependent components of the analgesia produced by athletic competition. The Journal of Pain 2 (1), 65–74. http://dx.doi.org/10.1054/jpai.2001.18236 pii:S1526-5900(01)42972-5.

Stirling, I., 1975. Factors affecting the evolution of social bahaviour in the Pinnipedia. In: Paper presented at the Rapports et Proces-Verbaux des Reunions (Denmark), vol. 169.

Stulp, G., Buunk, A.P., Verhulst, S., Pollet, T.V., 2015. Human height is positively related to interpersonal dominance in dyadic interactions. PLoS One 10 (2), e0117860.

Suttie, J., Fennessy, P., Lapwood, K., Corson, I., 1995. Role of steroids in antler growth of red deer stags. Journal of Experimental Zoology 271 (2), 120–130.

Suwa, G., Kono, R.T., Simpson, S.W., Asfaw, B., Lovejoy, C.O., White, T.D., 2009. Paleobiological implications of the Ardipithecus ramidus dentition. Science 326 (5949), 69–99. http://dx.doi.org/10.1126/science.1175824.

Thomas, J.R., French, K.E., 1985. Gender differences across age in motor performance: a meta-analysis. Psychological Bulletin 98 (2), 260.

Titze, I.R., 2000. Principles of Voice Production: National Center for Voice and Speech.

Trivers, R., 1972. Parental investment and sexual selection. In: Campbell, B. (Ed.), Sexual Selection and the Descent of Man. Aldinc, Chicago, pp. 136–179.

van Lawick-Goodall, J., 1968. The behaviour of free-living chimpanzees in the Gombe Stream Reserve. Animal Behaviour Monographs 1, 161. IN112.

Van Vugt, M., De Cremer, D., Janssen, D.P., 2007. Gender differences in cooperation and competition the Male-Warrior hypothesis. Psychological Science 18 (1), 19–23.

Van Wagenen, G., Hurme, V.O., 1950. Effect of testosterone propionate on permanent canine tooth eruption in the monkey (*Macaca mulatta*). Experimental Biology and Medicine 73 (2), 296–297.

von Rueden, C., Gurven, M., Kaplan, H., 2011. Why do men seek status? Fitness payoffs to dominance and prestige. Proceedings of the Royal Society B: Biological Sciences 278 (1715), 2223–2232. http://dx.doi.org/10.1098/rspb.2010.2145.

Walker, R.S., Bailey, D.H., 2013. Body counts in lowland South American violence. Evolution and Human Behavior 34 (1), 29–34. http://dx.doi.org/10.1016/j.evolhumbehav.2012.08.003.

Walker, R.S., Hill, K.R., Flinn, M.V., Ellsworth, R.M., 2011. Evolutionary history of hunter-gatherer marriage practices. PLoS One 6 (4), e19066.

Warner, J., Graham, K., Adlaf, E., 2005. Women behaving badly: gender and aggression in a military town, 1653–1781. Sex Roles 52 (5–6), 289–298. http://dx.doi.org/10.1007/s11199-005-2673-6.

Watson, N.V., Kimura, D., 1991. Nontrivial sex differences in throwing and intercepting: relation to psychometrically-defined spatial functions. Personality and Individual Differences 12 (5), 375–385.

Webster, D., 1998. Warfare and status rivalry: lowland Maya and Polynesian comparisons. In: Archaic States. School of American Research Press, Santa Fe, NM, pp. 464–470.

Welling, L.L.M., Persola, L., Wheatley, J.R., Cárdenas, R.A., Puts, D.A., 2013. Competition and men's face preferences. Personality and Individual Differences 54 (3), 414–419. http://dx.doi.org/10.1016/j.paid.2012.10.014.

Wells, J.C., 2012. Sexual dimorphism in body composition across human populations: associations with climate and proxies for short- and long-term energy supply. American Journal of Human Biology 24 (4), 411–419. http://dx.doi.org/10.1002/ajhb.22223.

West-Eberhard, M.J., 1983. Sexual selection, social competition, and speciation. The Quarterly Review of Biology 58 (2), 155–183.

White, T.D., Suwa, G., Simpson, S., Asfaw, B., 2000. Jaws and teeth of Australopithecus afarensis from Maka, Middle Awash, Ethiopia. American Journal of Physical Anthropology 111 (1), 45–68.

Wolff, S.E., Puts, D.A., 2010. Vocal masculinity is a robust dominance signal in men. Behavioral Ecology and Sociobiology 64 (10), 1673–1683. http://dx.doi.org/10.1007/s00265-010-0981-5.

Wood, B., Li, Y., Willoughby, C., 1991. Intraspecific variation and sexual dimorphism in cranial and dental variables among higher primates and their bearing on the hominid fossil record. Journal of Anatomy 174, 185.

Wrangham, R.W., Glowacki, L., 2012. Intergroup aggression in chimpanzees and war in nomadic hunter-gatherers: evaluating the chimpanzee model. Human Nature 23 (1), 5–29. http://dx.doi.org/10.1007/s12110-012-9132-1.

Wrangham, R.W., Wilson, M.L., Muller, M.N., 2006. Comparative rates of violence in chimpanzees and humans. Primates 47 (1), 14–26. http://dx.doi.org/10.1007/s10329-005-0140-1.

Wrangham, R.W., 1999. Evolution of coalitionary killing. American Journal of Physical Anthropology 110 (s 29), 1–30.

Wright, R., 1995. The biology of violence. The New Yorker 71 (3), 68–77.

Zilioli, S., Sell, A.N., Stirrat, M., Jagore, J., Vickerman, W., Watson, N.V., 2014. Face of a fighter: Bizygomatic width as a cue of formidability. Aggressive Behavior. http://dx.doi.org/10.1002/ab.21544.

Chapter 16

The Human Family: Evolutionary Origins and Adaptive Significance

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Humans are similar to most mammals in having intense maternal care including breastfeeding of an altricial (helpless) offspring, with some support from an assortment of other relatives. Beyond the shared mammal/primate commonality, however, humans exhibit a suite of highly unusual traits (Table 16.1). We are the only species characterized by the *combination* of: stable breeding bonds, extensive paternal effort in a multimale group, lengthy childhood, extended bilateral and multigenerational kin recognition, and controlled exchange of mates among kin groups (Alexander, 1979; 1990b; Chapais, 2008). These characteristics are important for understanding family relationships and the supporting cognitive, emotional, and physiological mechanisms; they also provide critical insights into the puzzle of human evolution.

In this chapter, I first review a general model for the evolution of human mating, parenting, and kinship patterns based on a process of runaway social selection (Alexander, 2006; Flinn and Alexander, 2007; Flinn et al., 2007). I then briefly evaluate the physiological mechanisms that underpin these central aspects of our sociality. The objectives include providing important information and ideas from biological and cultural anthropology that contribute to understanding the coevolution of the human family, life history, and the brain.

BRAIN, CHILDHOOD, AND FAMILY

Evolution of Mind in the Crèche of the Extended Family

Information processing (intelligence) and social communication (language) are core human adaptations. By all measures the human brain that enables these abilities is an astonishing organ. Its cerebral cortex comprises about 16 billion neurons of more than 100 different types, each of which are interlinked by about 1000 synapses, resulting in $>10^{15}$ connections working at rates of up to 10^{10} interactions per second (Edelman, 2006). Quantifying the transduction of these biophysical actions into specific mental activities—ie, thoughts and emotional feelings—is difficult, but it is likely that humans have more information processing capacity than any other species (Roth and Dicke, 2005).

The human brain evolved at a rapid pace: hominin cranial capacity tripled (from an average of about 450−1350 cc) in less than 2 million years (Lee and Wolpoff, 2003)—roughly 100,000 neurons and supportive cells per generation. Structural changes, such as increased convolutions, thickly myelinated cortical neurons, lateral asymmetries, increased von Economo neurons, expansion of the neocortex, and enhanced integration of the cerebellum also were significant (Fonseca-Azevedo and Herculano-Houzel, 2012; Schoenemann, 2006). In comparison with most other parts of the human genome, selection on genes involved with brain development was especially intense (Gilbert et al., 2005).

The human brain has high metabolic costs: about 50% of an infant's and 20% of an adult's energetic resources are used to support neurological activity (Elia, 1992; Kuzawa et al., 2009). Thoughts are not free; the high levels of glucose and other energetic nutrients required to fuel human cognition involve significant trade-offs (Campbell, 2010). Although the increase in energetic resources allocated to the brain was accompanied by a corresponding decrease in digestive tissue (Aiello and Wheeler, 1995), this does not explain what the selective pressures for enhanced information processing were, nor why the resources were

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00016-8

TABLE 16.1 Attributes of Humans that May Provide Clues to Our Evolution

1. Unusual speciation and extinction pattern
   a. No remaining ancestral species or side branches; apparent absence of adaptive radiation in *Homo* despite rapid evolutionary change
2. Rapid reduction of sexual dimorphisms (SDs)
   a. Canine SD reduced early (*Australopithecus*: Ward et al., 2001)
   b. Body size SD reduced later (*Homo erectus*; archaic *Homo sapiens*)
3. Unusual dentition
   a. Reduced canine size
   b. Small incisors
   c. Thick enamel on teeth
   d. Overall dental reduction
   e. Orthognathic face
   f. Protruding nose
4. Dietary niche
   a. Omnivorous catholic diet
   b. Variable environments
   c. Meat eating
   d. Hunting
   e. Extractive foraging of tubers, nuts, and other high-quality foods
   f. An array of corresponding cognitive and brain specializations, including those that support tool use for foods, and the development of folk biological knowledge (Atran, 1998)
   g. Cooking (Wrangham, 2009)
5. Habitual bipedal locomotion
   a. Lumbar curve, pelvis, bicondylar angle, knees
   b. Foot, arch, no grasping big toe
   c. Loss of climbing abilities
6. Unusual upper limbs
   a. Shortened, modified
   b. Accurate and powerful throwing of projectiles, and dodging, especially in males
   c. Fine manipulation with hands, digit proportions, innervation
7. Extraordinary mental capabilities
   a. Large brains, high metabolic cost (Fonseca-Azevedo and Herculano-Houzel, 2012)
   b. Unique aspects of gene and protein expression, transcription in brain cells
   c. Neuroanatomy; expanded neocortex, class of large and clustered spindle cells in anterior cingulate cortex, expansion of language-related neocortical areas, expansion and reorganization of some regions of the prefrontal cortex, development of Broca's area, and increased lateralization and gyrification (Allman, 1999)
   d. Consciousness and awareness of the self as a social being
   e. Theory of mind, and a complimentary set of sociocognitive competencies (Adolphs, 2003; see Geary, 2005; Geary and Huffman, 2002; for a taxonomy)
   f. Foresight, planning, scenario building, ability to mentally time travel; related to functioning of areas of the prefrontal cortex (Gallagher and Frith, 2003)
   g. Complex psyche, integrated cognitive aptitudes, flexible and relatively open learning
   h. Social emotions, guilt, embarrassment, pride, restraint, and concealment
   i. Humor (Alexander, 1987)
   j. Complex deception and deception detection
   k. Multiple order reasoning
   l. Imagination, fantasy
   m. Creativity
   n. Senses (vision, hearing) similar to other hominoids, some olfactory reduction
   o. Complex facial expressions
   p. Specific psychopathologies, eg, autism
8. Language, specific linguistic abilities
   a. Precocial language acquisition
   b. Open syntax, infinite combinations, and creativity
9. Culture
   a. Traditions, cumulative information building (Coe, 2003)
   b. Technology stemming from evolution of tool use and ecological dominance
   c. Social learning, complex imitation, emulation, teaching. The working memory and attentional control systems that support scenario building can also be used for the teaching and learning of culturally specific academic abilities, such as reading and writing (Geary, 2005).

TABLE 16.1 Attributes of Humans that May Provide Clues to Our Evolution—cont'd

10. Complex social groups
- **a.** Male kin- and nonkin coalitions (eg, Boehm, 1999; Chagnon, 1968)
- **b.** Complex systems of reciprocity (indirect and direct; eg, Alexander, 2006)
- **c.** Friendships
- **d.** Laws
- **e.** Ethics and moral systems (Alexander, 1987)
- **f.** Pervasive intra- and intergroup conflict, raiding, war (Bowles, 2009; Leblanc, 2003; Wrangham, 1999)
- **g.** Complex social play, team sports (Wagner et al., 2002)

11. Unusual patterns of kinship, parenting, and grandparenting
- **a.** Extensive kin networks
- **b.** Variable male philopatry (Murdock, 1949)
- **c.** Extensive parental care, including protection by males (Geary, 2010)
- **d.** Complex bonding, attachment, grief
- **e.** Long-term mating relationships, pair bonds
- **f.** Variable mating systems
- **g.** Parental and kin influence on mate choice
- **h.** Age- and sex-based division of labor, activity differences

12. Unusual life history
- **a.** Altricial young
- **b.** Rapid early brain growth, but continued throughout childhood (Deacon, 1997)
- **c.** Unusual patterning of growth and development, eg, pubertal growth spurt (Bogin, 1999)
- **d.** Menopause
- **e.** Precocial communication skills
- **f.** Extended childhood (Bogin, 1999)
- **g.** Adrenarche (Campbell, 2011)

13. Unusual sexual characteristics
- **a.** Concealed ovulation (Alexander and Noonan, 1979; Strassmann, 1981)
- **b.** Postreproductive sexual behavior
- **c.** Frontal copulation, kissing, foreplay
- **d.** Female orgasm
- **e.** Permanently enlarged breasts
- **f.** Large penis, lack of penis bone (baculum)
- **g.** Moderate testes
- **h.** Hymen

14. Other unusual physical characteristics
- **a.** Variation in skin, hair, facial appearance
- **b.** Melanin skin pigmentation
- **c.** Pale sclera
- **d.** Unusual importance of facial appearance for mate choice
- **e.** General hairlessness, but with sex-specific patterning, ever-growing hair on head

15. Unusual demographic and population traits
- **a.** Wide geographic distribution, large population size, rapid potential population growth

not reallocated to direct reproductive function. The obstetric difficulties associated with birthing a large-headed infant generate additional problems (Rosenberg and Trevathan, 2002). The selective advantages of increased intelligence must have been high to overcome these costs.

The human brain, in short, is a big evolutionary puzzle. It is developmentally and metabolically expensive. It evolved rapidly and consistently. And it enables unusual human cognitive abilities such as language, empathy, foresight, consciousness, mental time-travel, creativity, and theory of mind (ToM). Advantages of a larger brain may include enhanced information processing capacities to contend with ecological pressures that involve sexually dimorphic activities such as hunting and complex foraging (Kaplan and Robson, 2002). There is little evidence, however, of sufficient domain-specific enlargement of those parts of the brain associated with selective pressures from the physical environment, including subsistence activities (Adolphs, 2003; Geary and Huffman, 2002). Indeed, human cognition has little to distinguish itself in the way of specialized ecological talents. Our remarkable aptitudes for tool use and other technological behaviors depend primarily on general aptitudes for social learning and fluid intelligence (Geary, 2005; Blurton-Jones and Marlowe, 2002). A large brain may have been sexually selected because intelligence was an attractive trait for mate choice (Miller, 2000). However, there is little sexual dimorphism in encephalization quotient or intelligence

psychometrics (Geary, 2010), nor is there a clear reason why brains would have been a target for sexual selection driven by mate choice uniquely and consistently among hominins (but not in other species).

The human brain did not evolve as an isolated trait. Concomitant changes in other traits provide clues to what selective pressures were important during hominin evolution. Changes in life history patterns accompanied the evident increases in information processing and communication during the Pleistocene (Dean et al., 2001). Gestation (pregnancy) was lengthened, but the resultant infant was even more altricial (Rosenberg, 2004). Human infants must be carried, fed, and protected for a long period in comparison with those of other primates. And yet humans have shorter interbirth intervals than other hominoids (Robson and Wood, 2008). Human childhood and adolescence are also exceptionally lengthy (Del Giudice, 2009). This extension of the juvenile period appears costly in evolutionary terms. The delay of reproduction past 15 years of age or older involves prolonged exposure to extrinsic causes of mortality and longer generation intervals. Parental and other kin investment continues for an unusually long time, often well into adulthood and perhaps even after the death of the parents. Like the big brain, human life history is an evolutionary puzzle (Muehlenbein and Flinn, 2011).

Of course the child must accumulate energetic resources necessary for physical somatic growth. Whether the lengthening of the human juvenile period was an unavoidable response to an increasing shortage of calories, however, is uncertain. Other hominoids (chimpanzees, gorillas, orangutans) grow at similar overall rates, but mature earlier (Leigh, 2004). Increased body fat is associated with earlier puberty for girls, although psychological and genetic factors are also important, and the relation is not significant for boys (Lee et al., 2010). Moreover, low birth weight is associated with earlier puberty in some conditions (Karaolis-Danckert et al., 2009). The peculiarities of the human growth curve are also difficult to explain from a simple model of food scarcity—the general timing of growth spurts do not appear linked to a pattern of caloric surpluses. Hence although it is clear that human female growth and reproductive maturation are sensitive to fat accumulation (Ellison, 2001; Sloboda et al., 2007), the lengthening of the juvenile period during human evolution seems likely to have involved more than simple energetic constraints on physical growth.

Alternatively, the life history stage of human childhood could be an adaptation enabling cognitive development, including complex social skills and emotional regulation (Alexander, 1990a; Bjorklund and Pelligrini, 2002; Del Giudice, 2009; Flinn, 2004; Konner, 2010). The human child is an extraordinarily social creature, motivated by and highly sensitive to interpersonal relationships. Learning, practice, play, and experience are imperative for social success. The information processing capacity used for human social interactions is considerable, and perhaps significantly greater than that involved with foraging, locomotion, tool-making, and other subsistence skills (Schoenemann, 2006).

The child needs to master complex dynamic social tasks such as developing appropriate cognitive and emotional responses during interactions with peers and adults in the local community. The learning environments that facilitate and channel these aspects of human mental phenotypic plasticity appear to take on a special importance. Much of the data required for the social behavior necessary to be successful as a human cannot be "preprogrammed" into specific, detailed, fixed responses. Social cleverness in a fast-paced, cumulative cultural environment must contend with dynamic, constantly shifting strategies of friends and enemies, and hence needs information from experiential social learning and creative scenario-building (Flinn, 1997, 2006; Del Giudice, 2009).

To summarize our argument to this point, human childhood may be viewed as a life history stage that is necessary for acquiring the information and practice to build and refine the mental algorithms critical for negotiating the social relationships that are key to success in our species (Geary and Flinn, 2001; Muehlenbein and Flinn, 2011). Mastering the social environment presents special challenges for the human child. Social competence is difficult because the targets (other children and adults) are constantly changing and similarly equipped with theory of mind and other cognitive abilities. Selection for flexible cognitive problem solving would also enhance complementary development of more sophisticated ecological skills such as hunting and complex extractive foraging (Kaplan et al., 2000).

Human social relationships are especially complex because they involve extensive coalitions. We are extraordinarily cooperative, most exceptionally and importantly in regard to competition with other groups (Alexander, 1990b, 2006; Bowles, 2009; Flinn et al., 2005, 2012a,b). Humans are unique in being the only species that engages in group-against-group play, including team sports. This trait is cross-culturally universal, emerges early in child development, and often is the object of tremendous collective effort.

The family environment is a primary source and mediator of the ontogeny of information-processing abilities, including social competencies and group cooperation. Human biology has been profoundly affected by our evolutionary history as unusually social creatures, immersed in networks of family, kin, and dynamic, intercommunity coalitions.

THE HUMAN FAMILY

All human societies recognize kinship as a key organizational principle (Brown, 1991). All languages have kinship terminologies and concomitant expectations of obligations and reciprocity (Fortes, 1969; Murdock, 1949). Human kinship systems appear unique in the universal recognition of both bilateral (maternal and paternal) and multigenerational structure, with a general trend for co-residence of male kin, but a dozen or more major variants (Flinn and Low, 1986; Murdock, 1949). These aspects of human kinship link families into broader cooperative systems, and provide additional opportunities for alloparental care during the long social childhood. Three species-distinctive characteristics stand out as unusually important in this regard: (1) fathering, ie, extensive and specific investment by males, (2) grandparenting, and (3) networks of kinship that extend among communities and involve affinal (ties by marriage) and consanguineal (ties by blood) relationships (Walker et al., 2011; Macfarlan et al., 2014).

Fathers

Mammals that live in groups with multiple males—such as chimpanzees *(Pan troglodytes)*—usually have little or no paternal care, because the nonexclusivity of mating relationships obscures paternity (Alexander, 1990b; Clutton-Brock, 1991). In contrast, it is common for human fathers to provide protection, information, food, and social status for their children (Gray and Anderson, 2010). Paternal care in humans appears to be facilitated by relatively stable pair bonds, which not only involves cooperation between mates that often endures over the lifespan, but which requires an unusual type of cooperation among co-residing males—respect for each other's mating relationships.

The relatively exclusive mating relationships that are characteristic of most human societies (Flinn and Low, 1986) generate natural factions within the group. Mating relationships also can create alliances in human groups, linking two families or clans together (eg, Macfarlan et al., 2014). By way of comparison, in chimpanzee communities it is difficult for even the most dominant male to monopolize an estrous female; usually most of the males in a community mate with most of the females (Goodall, 1986; Mitani et al., 2010). Chimpanzee males in effect "share" a common interest in the community's females and their offspring. Human groups, in contrast, are composed of family units, each with distinct reproductive interests. Human males do not typically share mating access to all the group's females; consequently, there are usually reliable cues identifying which children are their genetic offspring, and which are those of other males (for exceptions see Walker et al., 2010). Because humans live in multimale groups, yet often maintain stable and exclusive mating relationships, the potential for fission along family lines is high. Still, human groups overcome this inherent conflict between family units to form large, stable coalitions—a "federation of families" (Chapais, 2013).

This unusual tolerance among co-residential males and their families stands in contrast to the norm of polygamous mate competition in group-living nonhuman primates. Selection pressures favoring such tolerance are uncertain, but likely involve the importance of both male parental investment and male coalitions for intraspecific conflict (Alexander, 1990b; Wrangham, 1999).

The advantages of intensive parenting, including paternal protection and other care, require a most unusual pattern of mating relationships: moderately exclusive pair bonding in multiple-male groups. No other primate (or mammal) that lives in large, cooperative multiple-reproductive-male groups has such extensive male parental care targeted at specific offspring. Competition for females in multiple-male groups usually results in low confidence of paternity (eg, bonobos and chimpanzees). Males forming exclusive pair bonds in multiple-male groups would provide cues of nonpaternity to other males, and hence place their offspring in great danger of infanticide (Hrdy, 1999). Paternal care is most likely to be favored by natural selection in conditions where males can identify their offspring with sufficient probability to offset the costs of investment, although reciprocity with mates is also likely to be involved (Geary and Flinn, 2001). Humans exhibit a unique "nested family" social structure, involving complex reciprocity among males and females to restrict direct competition for mates among group members.

It is difficult to imagine how this system could be maintained in the absence of another unusual human trait: concealed or cryptic ovulation (Alexander and Noonan, 1979). Human groups tend to be male philopatric (males tending to remain in their natal groups), resulting in extensive male kin alliances, useful for competing against other groups of male kin (Leblanc, 2003; Wrangham and Peterson, 1996). Females also have complex alliances, but usually are not involved directly in the overt physical aggression characteristic of intergroup relations (Campbell, 2002; Geary and Flinn, 2002). Relationships among human brothers and sisters are life-long even where residence is in different communities, in contrast with the absence of significant ties or apparent kin recognition after emigration in other hominoids. Parents, grandparents, and other kin may be especially important for the child's mental development of social and cultural maps because they can be relied upon as landmarks who provide relatively honest information. From this perspective, the evolutionary significance of the human family in regard to child development is viewed more as a nest from which social skills

may be acquired than just as an economic unit centered on the sexual division of labor (Flinn and Ward, 2005).

In summary, the care-providing roles of fathers are unusually important in humans, particularly in regard to protection and social power, but are flexible components of the human family and are linked with the roles of other relatives, including grandparents. In addition to the effects of direct parental care, paternity provides the basis for critical bilateral kinship links that extend across communities and generations. The neuroendocrine mechanisms that underpin human paternal and grandparental psychology are not well studied, but likely involve the common mammalian affiliative hormones oxytocin and arginine vasopressin, with additional influence from the hypothalamic–pituitary–gonadal and hypothalamic–pituitary–adrenal systems (Feldman, 2015, 2016; Gettler, 2014; Gray and Campbell, 2009; Pereira and Ferreira, 2016).

Grandparents

Grandparents and grandoffspring share 25% of their genes identical by descent, a significant opportunity for kin selection. Few species, however, live in groups with multiple overlapping generations of kin. Fewer still have significant social relationships among individuals two or more generations apart. Humans appear rather exceptional in this regard. Grandparenting is cross-culturally ubiquitous and pervasive (Murdock, 1967; Sear and Mace, 2005; Voland et al., 2005). Our life histories allow for significant generational overlaps, including an apparent extended postreproductive stage facilitated by the unique human physiological adaptation of menopause (Alexander, 1990b; Hawkes, 2003).

The significance of emotional bonding between grandparents and grandchildren is beyond doubt. The evolved functions are uncertain, but likely involve the exceptional importance of long-term extensive and intensive investment for the human child. The emotional and cognitive processes that guide grand-relationships must have evolved because they enhanced survival and eventual reproductive success of grandchildren. Leaving children with grandparents and other alloparental care providers allows parents to pursue productive activities that would otherwise be risky or difficult when encumbered with child care. In addition to the physical basics of food, protection, and hygienic care, psychological development of the human child is strongly influenced by the dynamics of the social environment (Konner, 2010). Grandparents may have knowledge and experience that are important and useful for helping grandchildren and other relatives survive and succeed in social competition (Coe, 2003; Hrdy, 2009). Humans are unusual in the critical role of kin in alloparental care and group coalitions.

Extended Kinship and Control of Mating Relationships

> *The direct application of theory from evolutionary biology to human marriage behavior and mating strategies is… not possible until the theory is modified to take into consideration the interdependency of individuals… and how their interdependency—coalition alliances—structures human mating behavior.*
>
> Chagnon (1968, p. 88)

Human communities are composed of families embedded in complex kin networks. The importance of kinship in traditional societies is paramount; social power is primarily contingent upon support from relatives. Complex kinship alliances are arguably the most distinguishing social behavioral characteristic of humans in preindustrial cultures, and yet it is rarely discussed in evolutionary psychology or evolutionary economics. Reciprocity in all its various guises (for review, see Alexander, 2006) is inextricably bound up with kinship in traditional societies, perhaps most importantly in regard to the control of mating in the institution of marriage. The vast majority of nonindustrial cultures in the Ethnographic Atlas (Murdock, 1967) have rules and preferences specifying what categories of relatives are appropriate for mating/marriage; these rules and preferences involve issues of resultant kin ties in addition to inbreeding avoidance. It is worth emphasizing that humans are unique in the regulation of mating relationships by kin groups. The reason for controlling who mates with whom is that humans are unique in the great importance of kinship ties for alliances among groups (eg, Macfarlan et al., 2014). Mates are usually obtained via strategic negotiation between kin groups. No other species exhibits systematic preferences and prohibitions for mating relationships between specific types of cousins.

If human ancestors had intergroup relations similar to that of chimpanzees (see Wilson et al., 2014; Wrangham, 1999; Wrangham and Peterson, 1996), it would have been difficult to make even the first steps toward cooperative alliances among males (and females) in different communities. An adult male attempting to establish a relationship with another group likely would be killed as he entered their range. Somehow our ancestors overcame such obstacles to the first steps toward the core human adaptation of intercommunity alliances. It is possible that our ancestors did not have hostile intergroup relations; this seems unlikely, however, on both empirical (Leblanc, 2003) and theoretical (Alexander, 1990b) grounds. The most potent factor driving the evolution of the psychological, social, and cultural mechanisms enabling the formation of increasingly large and complex coalitions was

competition with other such coalitions (Alexander, 1990b; Bowles, 2009; Flinn et al., 2005).

Recognition of kinship among individuals residing in different communities is key to intergroup cooperation. Humans are different from other hominoids in the coevolutionary development of (1) stable and moderately exclusive breeding bonds, (2) bilateral kin recognition and relationships, and (3) reciprocity and kin links among coresident and distant families (Alexander, 1990b; Chapais, 2013; Flinn et al., 2007). In short, the family was a critical building block for the evolution of more complex communities, with flexible residence choice with kin in multiple communities and apparent intentional cultivation of ties with relatives in multiple locations.

Hard evidence for the evolutionary trajectory of human family, kinship, and intergroup relations is scarce and indirect; neurobiology and physiology, however, provide some important clues.

NEUROLOGICAL AND PHYSIOLOGICAL MECHANISMS

Neuroendocrine systems may be viewed as complex sets of mechanisms designed by natural selection to communicate information among cells and tissues. Steroid and peptide hormones, associated neurotransmitters, and other chemical messengers guide behaviors of mammals in many important ways (Ellison, 2009; Lee et al., 2009; Panksepp, 2009). For example, analysis of patterns of hormone levels in naturalistic contexts can provide important insights into the evolutionary functions of the neuroendocrine mechanisms that guide human behaviors (eg, Ponzi et al., 2014). Here I focus on the neuroendocrine mechanisms that facilitate human family relationships.

Hormonal Basis for Attachment and Family Love

Some of the most precious human feelings are stimulated by close social relationships: a mother holding her newborn infant; brothers reunited after a long absence; lovers entangled in each other's arms. Natural selection has designed our neurobiological mechanisms, in concert with our endocrine systems, to generate potent sensations in our interactions with these most evolutionarily significant individuals. We share with our primate relatives the same basic hormones and neurotransmitters that underlie these mental gifts. But our unique evolutionary history has modified us to respond to different circumstances and situations; we are rewarded and punished for somewhat different stimuli than our phylogenetic cousins. Chimpanzees and humans share the delight—the sensational reward—when biting into a ripe, juicy mango. But the endocrine, neurological, and associated emotional responses of a human father to the birth of his child (eg, Storey et al., 2000) are likely to be quite different from those of a chimpanzee male. Happiness for a human has many unique designs, such as romantic love (Fisher et al., 2006), that involve modification of the neurological receptors and processors of shared endogenous messengers from our phylogenetic heritage.

Attachments or bonding are central in the lives of the social mammals. Basic to survival and reproduction, these interdependent relationships are the fabric of the social networks that permit individuals to maintain cooperative relationships over time. Although attachments can provide security and relief from stress, close relationships also exert pressures on individuals to which they continuously respond. It should not be surprising, therefore, that the neuroendocrine mechanisms underlying attachment and stress are intimately related to one another. And although more is known about the stress response systems than the affiliative systems, we are beginning to get some important insights into the neuroendocrine mechanisms that underpin human relationships (Feldman, 2015, 2016; Lee et al., 2009; Pereira and Ferreira, 2016; Rilling, 2013).

The mother-offspring relationship is at the core of mammalian life, and it appears that some of the biochemistry at play in the regulation of this intimate bond was also selected to serve in primary mechanisms regulating bonds between mates, paternal care, the family group, and even larger social networks. Although a number of hormones and neurotransmitters are involved in attachment and other components of relationships, the two peptide hormones, oxytocin (OT) and arginine-vasopressin (AVP), appear to be primary (Heinrichs et al., 2009; Lee et al., 2009; Seltzer et al., 2010), with dopamine, cortisol, and other hormones and neurotransmitters having mediating effects.

Experience affects the neuroendocrine systems involved in the expression of parental care. The HPA system of offspring during development is influenced by variation in maternal care, which then influences their maternal behavior as adults. Such changes involve the production of, and receptor density for, stress hormones and OT (Champagne and Meaney, 2001; Fleming et al., 1999). HPA-modulated hormones and maternal behavior are related in humans during the postpartum period (Fleming et al., 1997). During this time, cortisol appears to have an arousal effect, focusing attention on infant bonding. Mothers with higher cortisol levels were found to be more affectionate, more attracted to their infant's odor, and better at recognizing their infant's cry during the postpartum period.

fMRI studies of brain activity involved in maternal attachment in humans indicate that the activated regions are part of the reward system and contain a high density of receptors for OT and AVP (Bartels and Zeki, 2004;

Fisher et al., 2006; Swain et al., 2014). These studies also demonstrate that the neural regions involved in attachment activated in humans are similar to those activated in nonhuman animals. Among humans, however, neural regions associated with social judgment and assessment of the intentions and emotions of others exhibited some deactivation during attachment activities, suggesting possible links between psychological mechanisms for attachment and management of social relationships. Falling in love with a mate and affective bonds with offspring may involve temporary deactivation of psychological mechanisms for maintaining an individual's social "guard" in the complex reciprocity of human social networks. Dopamine levels are likely to be important for both types of relationship but may involve some distinct neural sites. It will be interesting to see what fMRI studies of attachment in human males indicate because that is where the most substantial differences from other mammals would be expected. Similarly, fMRI studies of attachment to mothers, fathers, and alloparental care providers in human children may provide important insights into the other side of parent–offspring bonding (Swain, 2011; Swain et al., 2014).

Androgens including testosterone also appear to be involved in the regulation of paternal behavior. For example, human fathers tend to have lower testosterone levels when they are involved in childcare activities (Berg and Wynne-Edwards, 2002; Fleming et al., 2002; Gray and Campbell, 2009; Kuzawa et al., 2009), although the relation with the key paternal role of offspring protection is uncertain. Human males stand out as very different from our closest relatives the chimpanzees in the areas of paternal attachment and investment in offspring. Investigation of the neuroendocrine mechanisms that underpin male parental behavior may provide important insights into these critical evolutionary changes.

The receptor density for OT and AVP in specific brain regions might provide the basis for mechanisms underlying other social behaviors. Other neurotransmitters, hormones, and social cues also are likely to be involved, but slight changes in gene expression for receptor density, such as those found between the meadow and prairie voles in the ventral palladium (located near the nucleus accumbens, an important component of the brain's reward system), might demonstrate how such mechanisms could be modified by selection (Lim et al., 2004). The dopamine D2 receptors in the nucleus accumbens appear to link the affiliative OT and AVP pair-bonding mechanisms with positive rewarding mental states (Aragona et al., 2006; Curtis and Wang, 2003). The combination results in the powerful addiction that parents have for their offspring (Love, 2014; Pereira and Ferreira, 2016).

Given the adaptive value of extensive biparental care and prolonged attachment found in the mating pair and larger family network, it is not surprising that similar neurohormonal mechanisms active in the maternal–offspring bond would also be selected to underlie these other attachments. Though there is some variation among species and between males and females, the same general neurohormonal systems active in pair-bonding in other species are found in the human (Wynne-Edwards, 2003; Panksepp, 2004; Lee et al., 2009; Ziegler, 2000). Androgen response to pair-bonding appears complex (eg, van der Meij et al., 2008), but similar to parent–offspring attachment in that pair-bonded males tend to have lower testosterone levels in nonchallenging conditions (Alvergne et al., 2009; Gray and Campbell, 2009). Moreover, males actively involved in caretaking behavior appear to have temporarily diminished testosterone levels and neurobiological changes (eg, Abraham et al., 2014).

Hormonal mechanisms for another key human adaptation, bonding among adult males forming coalitions—ie, "band of brothers"—is less well studied. Social effects such as victories against outsiders produce elevations in testosterone, but defeating friends does not (Flinn et al., 2012b). Changes in oxytocin are also contingent on relationships (De Dreu, 2012). Human males, moreover, may differentially respond to females contingent on whether the females are in a stable breeding bond with a close friend; males have lower T after interacting with wives of their relatives and friends (Flinn et al., 2012b). Involvement of the affiliative neuropeptides (OT and AVP) in relationships among adult males is unknown, and should be a key target for research efforts.

The challenge before human evolutionary biologists and psychologists is to understand how these general neuroendocrine systems have been modified and linked with other special human cognitive systems to produce the unique suite of human family behaviors. Analysis of hormonal responses to social stimuli may provide important insights into the selective pressures that guided the evolution of these key aspects of the human mind.

SUMMARY AND CONCLUDING REMARKS

Human childhood is a life history stage that appears necessary and useful for acquiring the information and practice to build and refine the mental algorithms critical for negotiating the social coalitions that are key to success in our species. Mastering the social environment presents special challenges for the human child. Social competence is difficult because the target is constantly changing and similarly equipped with theory of mind and other cognitive abilities. Family environment, including care from fathers and grandparents, is a primary source and mediator of the ontogeny of social competencies.

Social competence is developmentally expensive in time, instruction, and parental care. Costs are not equally justified for all expected adult environments. The human family may help children adjust development in response to environmental exigencies for appropriate trades-offs in life history strategies. An evolutionary developmental perspective of the family can be useful in these efforts to understand this critical aspect of a child's world by integrating knowledge of physiological causes with the logic of adaptive design by natural selection. Human biology has been profoundly affected by our evolutionary history as unusually social creatures, including, perhaps, a special reliance upon cooperative fathers, grandparents, and kin residing in other groups. Indeed, the mind of the human child may have design features that enable its development as a group project, guided by the multitudinous informational contributions of its ancestors and codescendants.

Understanding the coevolution of the core human adaptations of stable breeding bonds, biparental care, altricial infancy, prolonged childhood, complex social intelligence, extended kinship networks, and intergroup alliances presents difficult challenges for the social sciences. The inclusion of ideas and methods from anthropology and the life sciences may prove helpful, and hopefully make the task merrier.

REFERENCES

Abraham, E., Hendler, T., Shapira-Lichter, I., Kanat-Maymon, Y., Zagoory-Sharon, O., Feldman, R., 2014. Father's brain is sensitive to childcare experiences. Proceedings of the National Academy of Sciences of the United States of America 111 (27), 9792–9797.

Adolphs, R., 2003. Cognitive neuroscience of human social behavior. Nature Reviews, Neuroscience 4 (3), 165–178.

Aiello, L.C., Wheeler, P., 1995. The expensive-tissue hypothesis: the brain and the digestive system in human and primate evolution. Current Anthropology 36, 199–221.

Alexander, R.D., 1979. Darwinism and Human Affairs. University of Washington Press, Seattle.

Alexander, R.D., 1987. The Biology of Moral Systems. Aldine Press, Hawthorne, NY.

Alexander, R.D., 1990a. Epigenetic rules and Darwinian algorithms: the adaptive study of learning and development. Ethology and Sociobiology 11, 1–63.

Alexander, R.D., 1990b. How Humans Evolved: Reflections on the Uniquely Unique Species. Museum of Zoology (Special Publication No. 1). The University of Michigan, Ann Arbor.

Alexander, R.D., 2006. The challenge of human social behavior. Evolutionary Psychology 4, 1–32.

Alexander, R.D., Noonan, K.M., 1979. Concealment of ovulation, parental care, and human social evolution. In: Chagnon, N., Irons, W. (Eds.), Evolutionary Biology and Human Social Behavior. Duxbury Press, North Scituate.

Allman, J., 1999. Evolving Brains. Scientific American Library, New York.

Alvergne, A., Faurie, C., Raymond, M., 2009. Variation in testosterone levels and male reproductive effort: insight from a polygynous human population. Hormones and Behavior 56 (5), 491–497.

Aragona, B.J., Liu, Y., Yu, Y.J., Curtis, J.T., Detwiler, J.M., Insel, T.R., et al., 2006. Nucleus accumbens dopamine differentially mediates the formation and maintenance of monogamous pair bonds. Nature Neuroscience 9, 133–139.

Atran, S., 1998. Folk biology and the anthropology of science: cognitive universals and cultural particulars. Behavioral and Brain Sciences 21, 547–609.

Bartels, A., Zeki, S., 2004. The neural correlates of maternal and romantic love. NeuroImage 21, 1155–1166.

Berg, S.J., Wynne-Edwards, K.E., 2001. Changes in testosterone, cortisol, and estradiol levels in men becoming fathers. Mayo Clinic Proceedings 76, 582–592.

Bjorklund, D.F., Pellegrini, A.D., 2002. The Origins of Human Nature: Evolutionary Developmental Psychology. APA Press, Washington, DC.

Blurton-Jones, N.G., Marlowe, F.W., 2002. Selection for delayed maturity: does it take 20 years to learn to hunt and gather? Human Nature 13, 199–238.

Boehm, C., 1999. Hierarchy in the Forest: The Evolution of Egalitarian Behavior. Harvard University Press, Cambridge, MA.

Bogin, B., 1999. Evolutionary perspective on human growth. Annual Review of Anthropology 28, 109–153.

Bowles, S., 2009. Did warfare among ancestral hunter-gatherers affect the evolution of human social behaviors? Science 324, 1293–1298.

Brown, D.E., 1991. Human Universals. Temple University Press, Philadelphia.

Campbell, A., 2002. A Mind of Her Own: The Evolutionary Psychology of Women. Oxford University Press, London.

Campbell, B.C., 2010. Energetics and the human brain. In: Muhlenbein, M. (Ed.), Human Evolutionary Biology. Cambridge University Press, Cambridge, pp. 425–438.

Campbell, B.C., 2011. Adrenarche and middle childhood. Human Nature 22, 327–349.

Chagnon, N.A., 1968. Yanomamö: The Fierce People. Holt, Rinehart, & Winston, New York.

Champagne, F.A., Meaney, M.J., 2001. Like mother, like daughter: evidence for non-genomic transmission of parental behavior and stress responsivity. Progress in Brain Research 133, 287–302.

Chapais, B., 2008. Primeval Kinship: How Pair-bonding Gave Birth to Human Society. Harvard University Press, Cambridge, MA.

Chapais, B., 2013. Monogamy, strongly bonded groups, and the evolution of human social structure. Evolutionary Anthropology 22, 52–65.

Clutton-Brock, T.H., 1991. The Evolution of Parental Care. Princeton U. Press, Princeton, NJ.

Coe, K., 2003. The Ancestress Hypothesis: Visual Art as Adaptation. Rutgers University Press, New Brunswick.

Curtis, T.J., Wang, Z., 2003. The neurochemistry of pair bonding. Current Directions in Psychological Science 12 (2), 49–53.

De Dreu, C.K.W., 2012. Oxytocin modulates cooperation within and competition between groups: an integrative review and research agenda. Hormones and Behavior 61 (3), 419–428.

Deacon, T.W., 1997. The Symbolic Species: The Co-evolution of Language and the Brain. Norton, New York.

Dean, C., Leakey, M.G., Reid, D., Schrenk, F., Schwartz, G.T., Stringer, C., Walker, A., 2001. Growth processes in teeth distinguish

modern humans from *Homo erectus* and earlier hominins. Nature 414, 628–631.

Del Giudice, M., 2009. Sex, attachment, and the development of reproductive strategies. Behavioral and Brain Sciences 32, 1–21.

Edelman, G.M., 2006. Second Nature: Brain Science and Human Knowledge. Yale University Press, New Haven.

Elia, M., 1992. Organ and tissue contribution to metabolic rate. In: Kinner, J.M., Tucker, H.N. (Eds.), Energy Metabolism: Tissue Determinants and Cellular Corollaries. Raven Press, New York, pp. 61–79.

Ellison, P.T., 2001. On Fertile Ground, a Natural History of Human Reproduction. Harvard, Cambridge, MA.

Ellison, P.T., 2009. Social relationships and reproductive ecology. In: Ellison, P.T., Gray, P. (Eds.), Endocrinology of Social Relationships. Harvard University Press, Cambridge, MA, pp. 54–73.

Feldman, R., 2015. The adaptive human parental brain: implications for children's social development. Trends in Neuroscience 38 (6), 387–399. http://dx.doi.org/10.1016/j.tins.2015.04.004.

Feldman, R., 2016. The neurobiology of mammalian parenting and the biosocial context of human caregiving. Hormones and Behavior. http://dx.doi.org/10.1016/j.yhbeh.2015.10.001.

Fisher, H., Aron, A., Brown, L.L., 2006. Romantic love: a mammalian system for mate choice. Philosophical Transactions of the Royal Society B 361, 2173–2186.

Fleming, A.S., Steiner, M., Corter, C., 1997. Cortisol, hedonics, and maternal responsiveness in human mothers. Hormones and Behavior 32, 85–98.

Fleming, A.S., O'Day, D.H., Kraemer, G.W., 1999. Neurobiology of mother-infant interactions: experience and central nervous system plasticity across development and generations. Neuroscience and Biobehavioral Reviews 23, 673–685.

Fleming, A.S., Corter, C., Stallings, J., Steiner, M., 2002. Testosterone and prolactin are associated with emotional responses to infant cries in new fathers. Hormones and Behavior 42, 399–413.

Flinn, M.V., 2004. Culture and developmental plasticity: Evolution of the social brain. In: MacDonald, K., Burgess, R.L. (Eds.), Evolutionary perspectives on child development (Chapter 3). Sage, Thousand Oaks, CA, pp. 73–98.

Flinn, M.V., Alexander, R.D., 2007. Runaway social selection. In: Gangestad, S.W., Simpson, J.A. (Eds.), The Evolution of Mind. Guilford press, New York, pp. 249–255.

Flinn, M.V., Low, B.S., 1986. Resource distribution, social competition, and mating patterns in human societies. In: Rubenstein, D., Wrangham, R. (Eds.), Ecological Aspects of Social Evolution. Princeton University Press, Princeton, NJ, pp. 217–243.

Flinn, M.V., Ward, C.V., 2005. Evolution of the social child. In: Ellis, B., Bjorklund, D. (Eds.), Origins of the Social Mind: Evolutionary Psychology and Child Development. Guilford Press, London, pp. 19–44 (Chapter 2).

Flinn, M.V., Geary, D.C., Ward, C.V., 2005. Ecological dominance, social competition, and coalitionary arms races: why humans evolved extraordinary intelligence. Evolution and Human Behavior 26 (1), 10–46.

Flinn, M.V., Quinlan, R.J., Ward, C.V., Coe, M.K., 2007. Evolution of the human family: cooperative males, long social childhoods, smart mothers, and extended kin networks. In: Salmon, C., Shackelford, T. (Eds.), Family Relationships. Oxford University Press, Oxford, pp. 16–38 (Chapter 2).

Flinn, M.V., Duncan, C., Quinlan, R.L., Leone, D.V., Decker, S.A., Ponzi, D., 2012a. Hormones in the wild: monitoring the endocrinology of family relationships. Parenting: Science and Practice 12 (2), 124–133.

Flinn, M.V., Ponzi, D., Muehlenbein, M.P., 2012b. Hormonal mechanisms for regulation of aggression in human coalitions. Human Nature 22 (1), 68–88.

Flinn, M.V., 1997. Culture and the evolution of social learning. Evolution and Human Behavior 18 (1), 23–67.

Flinn, M.V., 2006. Evolution and ontogeny of stress response to social challenge in the human child. Developmental Review 26, 138–174.

Fonseca-Azevedo, K., Herculano-Houzel, S., 2012. Metabolic constraint imposes tradeoff between body size and number of brain neurons in human evolution. Proceedings of the National Academy of Sciences of the United States of America 109 (45), 18,571–18,576.

Fortes, M., 1969. Kinship and the Social Order. Aldine, Chicago, IL.

Gallagher, H.L., Frith, C.D., 2003. Functional imaging of 'theory of mind'. Trends in Cognitive Sciences 7, 77–83.

Geary, D.C., Flinn, M.V., 2001. Evolution of human parental behavior and the human family. Parenting: Science and Practice 1, 5–61.

Geary, D.C., Flinn, M.V., 2002. Sex differences in behavioral and hormonal response to social threat. Psychological Review 109 (4), 745–750.

Geary, D.C., Huffman, K.J., 2002. Brain and cognitive evolution: forms of modularity and functions of mind. Psychological Bulletin 128 (5), 667–698.

Geary, D.C., 2005. The Origin of Mind: Evolution of Brain, Cognition, and General Intelligence. American Psychological Association, Washington, DC.

Geary, D.C., 2010. Male, Female: The Evolution of Human Sex Differences, second ed. American Psychological Association, Washington, DC.

Gettler, L.T., 2014. Applying socioendocrinology to evolutionary models: fatherhood and physiology. Evolutionary Anthropology 23, 146–160.

Gilbert, S.L., Dobyns, W.B., Lahn, B.T., 2005. Genetic links between brain development and brain evolution. Nature Reviews Genetics 6 (7), 581–590.

Goodall, J., 1986. The Chimpanzees of Gombe: Patterns of Behavior. Belknap Press of Harvard University Press, Cambridge, MA.

Gray, P.B., Anderson, K.G., 2010. Fatherhood: Evolution and Human Paternal Behavior. Harvard University Press, Cambridge, MA.

Gray, P.B., Campbell, B.C., 2009. Human male testosterone, pair bonding and fatherhood. In: Ellison, P.T., Gray, P.B. (Eds.), Endocrinology of Social Relationships. Harvard University Press, Cambridge.

Hawkes, K., 2003. Grandmothers and the evolution of human longevity. American Journal of Human Biology 15, 380–400.

Heinrichs, M., Dawans, B.V., Domes, G., 2009. Oxytocin, vasopressin, and human social behavior. Frontiers in Neuroendocrinology 30 (4), 548–557.

Hrdy, S.B., 1999. Mother Nature: A History of Mothers, Infants, and Natural Selection. Pantheon, New York.

Hrdy, S.B., 2009. Mothers and Others: The Evolutionary Origins of Mutual Understanding. Harvard University Press, Cambridge.

Kaplan, H.S., Robson, A.J., 2002. The emergence of humans: the coevolution of intelligence and longevity with intergenerational transfers. Proceedings of the National Academy of Sciences of the United States of America 99 (15), 10221–10226.

Kaplan, H., Hill, K., Lancaster, J., Hurtado, A.M., 2000. A theory of human life history evolution: diet, intelligence and longevity. Evolutionary Anthropology 9, 156–183.

Karaolis-Danckert, N., Buyken, A.E., Sonntag, A., Kroke, A., 2009. Birth and early life influences on the timing of puberty onset: results from the DONALD (DOrtmund Nutritional and Anthropometric Longitudinally Designed) Study. American Journal of Clinical Nutrition 90 (6), 1559–1565.

Konner, M., 2010. The Evolution of Childhood: Relationships, Emotion, Mind. Harvard University Press, Cambridge, MA.

Kuzawa, C.W., Gettler, L.T., Muller, M.N., McDade, T.W., Feranil, A.B., 2009. Fatherhood, pairbonding and testosterone in the Philippines. Hormones and Behavior 56 (4), 429–435.

Leblanc, S.A., 2003. Constant Battles: The Myth of the Peaceful, Noble Savage. St. Martin's Press, New York.

Lee, S.H., Wolpoff, M.H., 2003. The pattern of evolution in Pleistocene human brain size. Paleobiology 29, 186–196.

Lee, H.-J., Macbeth, A.H., Pagani, J., Young 3rd, W.S., 2009. Oxytocin: the great facilitator of life. Progress in Neurobiology 88 (2), 127–151.

Lee, J.M., Kaciroti, N., Appugliese, D., Corwyn, R.F., Bradley, R.H., Lumeng, J.C., 2010. Body mass index and timing of pubertal initiation in boys. Archives of Pediatrics and Adolescent Medicine 164 (2), 116–123.

Leigh, S.R., 2004. Brain growth, cognition, and life history in primate and human evolution. American Journal of Primatology 62, 139–164.

Lim, M.M., Wang, Z., Olazábal, D.E., Ren, X., Terwilliger, E.F., Young, L.J., 2004. Enhanced partner preference in a promiscuous species by manipulating the expression of a single gene. Nature 429 (6993), 754–757.

Love, T.M., 2014. Oxytocin, motivation and the role of dopamine. Pharmacology Biochemistry and Behavior 119, 49–60.

Macfarlan, S.J., Walker, R.S., Flinn, M.V., Chagnon, N.A., 2014. Lethal coalitionary aggression and long-term alliances among Yanomamö men. Proceedings of the National Academy of Sciences of the United States of America 111 (52), 16662–16669.

Miller, G.E., 2000. The Mating Mind: How Sexual Choice Shaped the Evolution of Human Nature. Doubleday, New York.

Mitani, J.C., Watts, D.P., Amsler, S.J., 2010. Lethal intergroup aggression leads to territorial expansion in wild chimpanzees. Current Biology 20 (12), R507–R508.

Muehlenbein, M., Flinn, M.V., 2011. Pattern and process of human life history evolution. In: Flatt, T., Heyland, A. (Eds.), Oxford Handbook of Life History. Oxford University Press, Oxford, pp. 153–168 (Chapter 23).

Murdock, G.P., 1949. Social Structure. Macmillan, New York.

Murdock, G.P., 1967. Ethnographic Atlas. University of Pittsburgh Press, Pittsburgh, PA.

Panksepp, J., 2004. Affective Neuroscience: The Foundations of Human and Animal Emotions. Oxford University Press, New York.

Panksepp, J., 2009. Primary Process Affects and Brain Oxytocin. Biological Psychiatry 65, 725–727. http://dx.doi.org/10.1016/j.biopsych.2009.02.004.

Pereira, M., Ferreira, A., 2016. Neuroanatomical and neurochemical basis of parenting: dynamic coordination of motivational, affective and cognitive processes. Hormones and Behavior. http://dx.doi.org/10.1016/j.yhbeh.2015.08.005.

Ponzi, D., Muehlenbein, M.P., Sgoifo, A., Geary, D.C., Flinn, M.V., 2014. Day-to-day variation of salivary cortisol and dehydroepiandrosterone (DHEA) in children from a rural Dominican community. Adaptive Human Behavior and Physiology 1, 12–24.

Rilling, J.K., 2013. The neural and hormonal bases of human parental care. Neuropsychologia 51 (4), 731–747.

Robson, S.L., Wood, B., 2008. Hominin life history: reconstruction and evolution. Journal of Anatomy 212 (4), 394–425.

Rosenberg, K., Trevathan, W., 2002. Birth, obstetrics and human evolution. BJOG: An International Journal of Obstetrics and Gynecology 109 (11), 1199–1206.

Rosenberg, K., 2004. Living longer: information revolution, population expansion, and modern human origins. Proceedings of the National Academy of Sciences of the United States of America 101 (30), 10847–10848.

Roth, G., Dicke, U., 2005. Evolution of the brain and intelligence. Trends in Cognitive Sciences 9 (5), 250–257.

Schoenemann, P.T., 2006. Evolution of the size and functional areas of the human brain. Annual Review of Anthropology 35, 379–406.

Sear, R., Mace, R., 2008. Who keeps children alive? A review of the effects of kin on child survival. Evolution and Human Behavior 29 (1), 1–18.

Seltzer, L.J., Ziegler, T.E., Pollak, S.D., 2010. Social vocalizations can release oxytocin in humans. Proceedings of the Royal Society B. http://dx.doi.org/10.1098/rspb.2010.0567.

Sloboda, D.M., Hart, R., Doherty, D.A., Pennell, C.E., Hickey, M., 2007. Age at menarche: influences of prenatal and postnatal growth. Journal of Clinical Endocrinology and Metabolism 92, 46–50.

Storey, A.E., Walsh, C.J., Quinton, R.L., Wynne-Edwards, K.E., 2000. Hormonal correlates of paternal responsiveness in new and expectant fathers. Evolution and Human Behavior 21, 79–95.

Strassmann, B.I., 1981. Sexual selection, paternal care, and concealed ovulation in humans. Ethology and Sociobiology 2, 31–40.

Swain, J.E., Kim, P., Spicer, J., Ho, S.S., Dayton, C.J., Elmadih, A., Abel, K.M., 2014. Approaching the biology of human parental attachment: brain imaging, oxytocin and coordinated assessments of mothers and fathers. Brain Research 1580, 78–101. http://dx.doi.org/10.1016/j.brainres.2014.03.007.

Swain, J.E., 2011. The human parental brain: in vivo neuroimaging. Progress in Neuro-Psychopharmacology and Biological Psychiatry 35, 1242–1254.

van der Meij, L., Buunk, A.P., van de Sande, J.P., Salvador, A., 2008. The presence of a woman increases testosterone in aggressive dominant men. Hormones and Behavior 54, 640–644.

Voland, E., Chasiotis, A., Schiefenhövel, W., 2005. Grandmotherhood: The Evolutionary Significance of the Second Half of Female Life. Rutgers University Press, New Brunswick, NJ.

Wagner, J.D., Flinn, M.V., England, B.G., 2002. Hormonal response to competition among male coalitions. Evolution and Human Behavior 23 (6), 437–442.

Walker, R.S., Flinn, M.V., Hill, K., 2010. The evolutionary history of partible paternity in lowland South America. Proceedings of the National Academy of Sciences of the United States of America 107 (45), 19195–19200.

Walker, R.S., Hill, K., Flinn, M.V., Ellsworth, R., 2011. Evolutionary history of hunter-gatherer marriage practices. PLoS One 6 (4), e19066.

Ward, C.V., Leakey, M., Walker, A., 2001. Morphology of *Australopithecus anamensis* from Kanapoi and Allia Bay, Kenya. Journal of Human Evolution 41, 255–368.

Wilson, M.L., Boesch, C., Fruth, B., Furuichi, T., Gilby, I.C., Hashimoto, C., Hobaiter, C.L., Hohmann, G., Itoh, N., Koops, K., Lloyd, J.N., Matsuzawa, T., Mitani, J.C., Mjungu, D.C., Morgan, D., Muller, M.N., Mundry, R., Nakamura, M., Pruetz, J., Pusey, A.E., Riedel, J., Sanz, C., Schel, A.M., Simmons, N., Waller, M., Watts, D.P., White, F., Wittig, R.M., Zuberbühler, K., Wrangham, R.W., September 18, 2014. Lethal aggression in Pan is better explained by adaptive strategies than human impacts. Nature 513 (7518), 414–417. http://dx.doi.org/10.1038/nature13727.

Wrangham, R.W., Peterson, D., 1996. Demonic Males. Houghton Mifflin Company, New York.

Wrangham, R.W., 1999. Evolution of coalitionary killing. Yearbook of Physical Anthropology 42, 1–30.

Wrangham, R.W., 2009. Catching Fire: How Cooking Made Us Human. Basic Books, New York.

Wynne-Edwards, K.E., 2003. From dwarf hamster to daddy: the intersection of ecology, evolution, and physiology that produces paternal behavior. In: Slater, P.J.B., Rosenblatt, J.S., Snowden, C.T., Roper, T.J. (Eds.), Advances in the Study of Behavior, 32. Academic Press, San Diego, CA, pp. 207–261.

Ziegler, T.C., 2000. Hormones associated with non-maternal infant care: a review of mammalian and avian studies. Folia Primatologica 71 (1–2), 6–21.

FURTHER READING

Bissonnette, A., Perry, S., Barrett, L., Mitani, J., Flinn, M.V., Gavrilets, S., De Waal, F.B., 2015. Coalitions in theory and reality: a review of pertinent variables and processes. Behaviour 152 (1), 1–56.

Feldman, R., Gordon, I., Zagoory-Sharon, O., 2011. Maternal and paternal plasma, salivary, and urinary oxytocin and parent-infant synchrony: considering stress and affiliation components of human bonding. Developmental Science 14 (4), 752–761.

Feldman, R., Zagoory-Sharon, O., Weisman, O., Schneiderman, I., Gordon, I., Maoz, R., Shalev, I., Ebstein, R.P., 2012. Sensitive parenting is associated with plasma oxytocin and polymorphisms in the *OXTR* and *CD38* genes. Biological Psychiatry 72, 175–181.

Fernandez-Duque, E., Valeggia, C.R., Mendoza, S.P., 2009. The biology of paternal care in human and nonhuman primates. Annual Review of Anthropology 38, 115–130.

Flinn, M.V., Leone, D.V., 2006. Early trauma and the ontogeny of glucocorticoid stress response: grandmother as a secure base. Journal of Developmental Processes 1 (1), 31–68.

Flinn, M.V., Leone, D.V., 2009. Alloparental care and the ontogeny of glucocorticoid stress response among stepchildren. In: Bentley, G., Mace, R. (Eds.), Substitute Parents, Biosocial Society Symposium Series. Berghahn Books, Oxford, pp. 212–231.

Flinn, M.V., Ward, C.V., 2015. Hormones and the evolution of human sociality. In: Buss, D. (Ed.), Handbook of Evolutionary Psychology, second ed. Wiley, New York (Chapter 24).

Flinn, M.V., Nepomnaschy, P., Muehlenbein, M.P., Ponzi, D., 2011. Evolutionary functions of early social modulation of hypothalamic-pituitary-adrenal axis development in humans. Neuroscience and Biobehavioral Reviews 35 (7), 1611–1629.

Geary, D.C., Bjorklund, D.F., 2000. Evolutionary developmental psychology. Child Development 71 (1), 57–65.

Heinrichs, M., Domes, G., 2008. Neuropeptides and social behaviour: effects of oxytocin and vasopressin in humans. Progress in Brain Research 170, 337–350.

Hill, K., Hurtado, A., 1996. Ache Life History: The Ecology and Demography of a Foraging People. Aldine de Gruyter, Hawthorne, NY.

Isler, K., van Schaik, C.P., 2009. The expensive brain: a framework for explaining evolutionary changes in brain size. Journal of Human Evolution 57, 392–400.

Joffe, T.H., 1997. Social pressures have selected for an extended juvenile period in primates. Journal of Human Evolution 32, 593–605.

Konner, M., 1991. Childhood. Little, Brown, Boston, MA.

Nepomnaschy, P., Flinn, M.V., 2008. Early life influences on the ontogeny of neuroendocrine stress response in the human child. In: Ellison, P., Gray, P. (Eds.), The Endocrinology of Social Relationships. Harvard University Press, Cambridge, MA, pp. 364–382 (Chapter 16).

Shonkoff, J.P., Boyce, W.T., McEwen, B.S., 2009. Neuroscience, molecular biology, and the childhood roots of health disparities: building a new framework for health promotion and disease prevention. JAMA 301 (21), 2252–2259.

Uvnas-Moberg, K., 1998. Oxytocin may mediate the benefits of positive social interaction and emotions. Psychoneuroendocrinology 23, 819–835.

Walker, R.S., Beckerman, S., Flinn, M.V., Gurven, M., von Reuden, C.R., Kramer, K.L., Greaves, R.D., Córdoba, L., Hagen, E.H., Koster, J.M., Sugiyama, L., Hunter, T.E., Hill, K.R., 2013. Living with kin in lowland horticultural societies. Current Anthropology 54 (1), 96–103.

Walvoord, E.C., 2010. The timing of puberty: is it changing? Does it matter? Journal of Adolescent Health 47 (5), 433–439.

Young, L., Wang, Z., Insel, T.R., 2002. Neuroendocrine bases of monogamy. In: Cacioppo, J.T., Berntson, G.G., Adolphs, R., Carter, C.S., Davidson, R.J., McClintock, M.K., et al. (Eds.), Foundations in Social Neuroscience. MIT Press, Cambridge, MA, pp. 809–816.

Chapter 17

Biological Future of Humankind: Ongoing Evolution and the Impact of Recognition of Human Biological Variation

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BASIC PRINCIPLES OF HUMAN ADAPTATION

Humans are biological systems (Strzałko et al., 1980). To understand their future, one has to consider how they were shaped by the past evolutionary events, and how forces of evolution influence them now. Biological variation is a necessary phenomenon for evolution both as its substrate and its result. Biological variation occurs every generation due to gene recombination, de novo mutations, epigenetic effects, and adaptive responses of phenotypes. Since environmental conditions vary from generation to generation, too, there is a constant change in the distribution of biological characteristics of people in populations. Evolution is a common phenomenon, not just a creator of new species. It is a dynamic process because of reproduction. Old individuals die and then their phenotypic characters vanish. The only way that these phenotypes can persist over time is to recreate them every generation from genetic information unraveling through epigenetic mechanisms during individual ontogeny. Therefore, no "old" characteristics persist in populations. All characteristics of a new generation are "new," but some resemble characteristics of previous generations by the virtue of still being useful in new environmental conditions.

Multicellular organisms are complex systems and their particular characteristics must be attuned to working together so as to ensure reproductive success of their bearers. Thus, if any character changes, others must change, too. Change, or variability, is the core property of life.

For practical reasons, infinitely variable individuals are allocated to categories. Therefore, categories contain objects that are not precisely identical. Yet the categories are often used as units of scientific analyses.

The general principles mentioned earlier are pertinent to human biology and its applications in medical practice. Human bodies are a product of organic evolution. Therefore, biochemical and physiological processes that create and maintain their structures and functions are products of adaptations to conditions experienced by ancestral generations. They are, however, continuously modified by epigenetic processes using inherited information in newly occurring environmental conditions and by random errors in copying genetic information passed on from parents to offspring. Many of these errors are biologically neutral—changes of single nucleotides in DNA sequences—but some may be detrimental if they alter actively transcribed code for a biochemically active molecule so that it cannot be used in processes sustaining life of an individual or may affect its ability to produce offspring. Such errors will not be passed on to next generations because an individual affected will not have progeny. This differentiation of reproductive success of individuals with different genes does not need to be categorical. Genes that lower the ability to survive only to a certain extent and genes that affect fertility only somewhat may be passed to next generations, but at a rate lower than genes that do not affect survival or

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00017-X

fertility. The process of differential contribution of genes to new generations is called natural selection. It operates continuously, most of its actions being a simple cleaning of detrimental mutations. It may produce phenotypic changes when, rarely, a mutation occurs that enhances reproductive success or when living conditions alter so that effects of particular genes acquire a different relation with the environment producing phenotypic changes that affect chances of their reproduction.

Since evolution is now well recognized by life sciences as a real phenomenon, approaches to human health need to take it into account. This is done by the recently established discipline of evolutionary medicine. At its outset it has been defined as the "enterprise of trying to find evolutionary explanations for vulnerabilities to disease" (https://sites.google.com/site/evolutionarymedicine/, accessed 15.10.15.).

Evolutionary approaches to medical problems use the understanding of past adaptations to indicate their mismatches with the present-day living conditions and to suggest remediation of such mismatches. The understanding of how current changes to the genetic endowment affect human life and health requires further attention, and we propose to expand evolutionary medicine attention in this direction. This chapter attempts to show very recent changes in human variation using already published evidence.

RECENT CHANGE OF HUMAN ECOLOGY

The exact date of the appearance of humans on Earth, whose bodies were essentially the same as the bodies of a recent people, is still debated by paleoanthropologists (Henneberg, 2001a; Collard and Wood, 2015). It is widely accepted that since the advent of food production (agriculture and animal husbandry) humans and their populations were actors in the history that led to our existence. Since people were increasingly controlling their environment over the past 10,000 years or so, it can be expected that they were not so much adapting to their living conditions as adapting conditions to themselves; ie, managing their environment. This management, however, has not been fully conscious and thus produced new pressures on biological characteristics of human bodies. During this period, we were adapting to a human-transformed environment.

In general terms, we were protecting our bodies against climatic conditions by building shelters, producing clothing, and using fire; we changed profoundly our diets, moving them away from protein-rich but unreliable supplies obtained through gathering and hunting toward carbohydrate-rich and regular meals, which were usually reliable but subject to periodical shortages. Reliance on agricultural products required the preparation of fields, storage, and processing of plant materials harvested in substantial quantities, while animal husbandry required processing of meat and dairy products for future use. All those requirements could only be met by large amounts of labor, requiring high levels of skills but not much of physical strength. Endurance rather than explosive power became important. Finally, by allowing large sedentary populations to exist, we have created a reservoir of infectious diseases and doubled fertility rates. In terms of physical structure, adaptive pressures favoring large strong bodies were replaced by pressures toward energetically more efficient gracile bodies. The situation briefly described earlier in this chapter led to the generalized trend toward reductions in structures of the human body and changes in its immune responses. It has been suggested as early as the 1960s (Brace, 1964) that the most probable effects of random mutations are losses of structure or function.

STRUCTURAL REDUCTION OF HUMAN MORPHOLOGY

Among reductions in anatomical structures, the best described are gracilization, microcranialization, and dental reductions. Gracilization (Debetz, 1960, 1964; Schwidetzky, 1962) means loss of robusticity of the skeleton and is evidenced by decreasing stature, reduced width of long bones in relation to their length, and less relief on sites of muscle attachment to bones (entheses). It cannot be excluded that omnipresence of infectious diseases, especially chronic infections such as tuberculosis (Holloway et al., 2011) and malaria is partly responsible for poor child growth leading to reduced stature and less muscle mass. The process of gracilization has only been reversed in developed economies in the last few generations when improved sanitation and nutrition removed impediments to growth (Henneberg and van den Berg, 1990; Henneberg, 2001b). Microcranialization (Table 17.1), a decrease of the brain size during the time of the development of major civilizations, is not as counterintuitive as it appears at the first glance when it is considered that control of skeletal muscle activities is one of the major functions of the brain. With gracilization, decreased skeletal muscle mass has been reflected in smaller size of the brain (Henneberg, 1988, 1998).

One of the well-known short-term trends in human anatomy has been brachycephalization. Braincases in certain regions of the world, most notably the Central Europe, changed the ratio of their maximum width to maximum length in the time span of some 800 years. In Europe, including also Mediterranean parts of Africa and Asia, the ratio (called the Cranial Index) changed from 76% in the early Middle Ages to 81% in the 20th century AD (Henneberg, 1988). A change of 5 percentage units is very

TABLE 17.1 Rates of Change of Human Cranial Characters Measured in Darwins: $(\ln X_2 - \ln X_1)/T$

Trait	Initial Value	Final Value	Period (Ma)	Rate (Darwins)
Cranial Capacity				
Australopithecus africanus—Homo sapiens	450 mL	1350 mL	3.40	+0.32
H. sapiens in Europe	1456 mL	1350 mL	0.007	−10.80
Cranial Index				
Au. africanus—H. sapiens	70.0%	75.0%	2.50	+0.03
H. sapiens in Europe	73.0%	80.5%	0.0015	+65.20

X_1, initial state of character X; X_2, final state of character X; T-time in years.
Data from Henneberg, M., 2006. The rate of human morphological microevolution and taxonomic diversity of hominids (Essays in memory of Andrzej Wiercinski). Studies in Historical Anthropology 4, 49–59.

significant considering that the standard deviation of this ratio is only about 3%. A number of hypothetical explanations of this process have been offered (Hennebrg, 1976); none, however, has been conclusively tested to be true. A correlation has been found between the value of the Cranial Index and susceptibility to measles (Henneberg et al., 1984). A rather curious result from the biological point of view, though fully statistically sound and significant. A possible explanation is that organisms with different rates of growth of skeletal length (including skull base length) through interchondral ossification and braincase width through intermembranous ossification have somewhat different physiologies related to greater or lower immunity to a common disease. Between the early Middle Ages and modern times, population density and population mobility changes as well as sanitation and medical care may have influenced the epidemiology of measles to the extent of the higher reproductive performance of individuals with different head shapes. The final explanation of the process of brachycephalization is still not available.

Dental reductions are manifest in both the agenesis of certain teeth becoming more common through time—this is especially true with regard to third molars (wisdom teeth), but also lateral incisors and premolars—and the reduction of tooth size (Brace et al., 1987). Dental reductions can be attributed to improvements in preparation of foods making chewing an easy task. This is abundantly evidenced by decreasing through time the degree of tooth attrition. This decrease progressed to such an extent that at present some dentists consider tooth wear to be a pathological sign. Dental reductions were accompanied by increases in oral diseases, especially dental caries and periodontal disease (Scott and Irish, 2013). This testifies to the significant change in the microflora of the oral cavity and its interaction with physiological processes producing dental film, an organic layer protecting tooth enamel against decay (Kaidonis and Townsend, 2016). We are beginning to understand the evolution of the oral microflora based on data from ancient calculus (Warinner et al., 2014). The whole microbiome of the human body is changing. These changes and their impact are discussed in the next section. Periodontal disease is related to cardiovascular diseases (Lockhart et al., 2012) thus showing that changes in the oral cavity are indicative of changes in other body systems.

CHANGES IN BODY HEIGHT

In the past 100 years, or so, increases in body size were abundantly reported. Reports from Europe and North America indicate increases at rates 100–150 mm per century (Van Wieringen, 1986). These were typically attributed to improvements in living conditions (Komlos, 1994), especially nutrition and sanitation. In those countries of the Southern Hemisphere where specific populations had living conditions, and their changes, similar to those in Europe—European South Africans and European Australians—stature increases were of a much smaller magnitude and happened at a much slower rate: about 50 mm per century (Henneberg and van den Berg, 1990; Henneberg, 2001b). Finally, lacks of increases in some states or countries went unreported due to the "publication bias" (if we found no change we have nothing to report). Since extremely differing living conditions produce only about one standard deviation difference in stature (~60–70 mm) among people of the same population (Bielicki and Welon, 1982; Henneberg and Louw, 1998; Henneberg and LaVelle, 1999), it is difficult to interpret changes by as much as 150 mm, or more, as just a simple effect of improving living conditions. Improving at a similar rate living conditions of European Australians or "White" South Africans are consistent with about one standard deviation difference between the poorest and the richest people of the same population, the remainder of changes reported from the Northern Hemisphere requires additional explanation. A likely explanation is the

appearance during the growth of these people of some changed interaction between growth hormone and its receptors in growth plates of long bones (Henneberg, 2001b). Whether this phenomenon resulted from external administration of additional doses of growth hormones (Moizheson-Blank, 1991) or from some alteration of genetic endowment over the life of three to four generations is still to be found. It is known that use of antibiotics increases body size of domestic animals (Meek et al., 2015). It may be that at least a part of body size increases resulted from the use of antibiotics for humans. Due to climatic differences between the areas of the Northern and the Southern Hemisphere inhabited by people of European origin, it may be that prevalence of infectious diseases being treated with antibiotics was greater in the North than in the South. Thus the exposure of children to antibiotics was greater in the North. Results of this significant increase of body size in populations of some developed countries may have gone beyond "bigger is better" and are verging on the phenomenon of hypermorphosis (Bogin et al., 1992; Shea, 1989) that is such an extensive increase in body size that it changes its proportions and may start posing biomechanical and circulatory problems. Blood pressure is positively correlated with body height (Ulijaszek and Henneberg, 2012) since the heart must produce greater pressure to deliver blood to the brain located higher above the ground (or rather above the heart itself). In the first decade of the 21st century, increases in body height ceased in many countries (Staub and Rühli, 2013).

CHANGES OF ANATOMICAL STRUCTURES

Changes occurring at the scale of decades or centuries are not limited to overall body size. They also occur in specific anatomical details. One of the simplest ones is the disappearance of the thyroidea ima artery, a small branch of the aorta (Bhatia et al., 2005). The other structural loss is the lack of closure of the sacral canal known as the *spina bifida occulta*. The prevalence of the open sacral canal at the S1 level doubled since the times of the Roman Empire (Henneberg and Henneberg, 1999) and even within the 20th century the prevalence continued to increase (Lee et al., 2011; Solomon et al., 2009). Contrary to the disappearance of certain structures, some are appearing more frequently. The best-documented example is the persistence of the median artery of the forearm into adulthood. Its prevalence more than doubled during the 20th century (Henneberg and George, 1995). It seems that this trend is a result of changes in the embryonic development that allow embryonic conditions to persist into postnatal life. Another example of such phenomenon is increasing prevalence of tarsal coalitions (Solomon et al., 2003). Changing frequencies of multiple renal arteries and veins (Satyapal et al., 2000; Satyapal, 2003) may be a result of altered level of the ascent of kidneys in an embryo. It is possible that many other anatomical variants change their prevalence in time spans of decades; such changes need to be documented.

Together, described changes in anatomical structures suggest alterations of the embryonic development, as some of them are retentions of embryonic structures and others represent incomplete development. At present it is difficult to ascertain whether the embryonic development is simplified or accelerated. More emphasis needs to be put by anatomists, clinicians, and biologists on observing anatomical variations, as they may be indicative of general trends in human development.

CHANGES IN NATURAL SELECTION

Natural selection operates through differential reproduction of different alleles. Altered opportunity of an allele to be passed to the next generation may happen at the time genetic material is halved in the meiosis and packaged into gametes. Gametes may have different viability or motility depending on the hereditary material they carry (Imsland et al., 2012; Jumeau et al., 2015). They may also have differential ability to fertilize or become fertilized. The development of the embryo and then the fetus is strongly controlled by genetic program that interacts with maternal physiology and the intrauterine environment. Any errors in the inherited developmental program may terminate the life of an embryo or a fetus. This happens quite often (McNair and Altman, 2012; Betts and King, 2001) and clearly does not allow the genes of that fetus to be passed on to the next generation. Postnatal ontogeny is still controlled by genetic programs interacting with more complex extrauterine environment that exposes infants and children to a host of pathogens and potentially traumatic situations. A death at this stage of ontogeny, if in any form related to the genetic endowment, will prevent passing of those genes to the next generation. Finally, adults may differ in their fecundity and fertility due to genetic reasons that will differentiate reproduction of relevant alleles. It is difficult to measure amounts of selection acting against specific alleles or favoring other alleles but the total opportunity for selection is easy to assess since it is a result of the variance in reproductive performance of individuals (Crow, 1958). It is practical to measure it as a sum of the variance in mortality and in fertility. It is obvious that only the heritable portion of reproductive variance can have selective effects:

$$I = Vh^2,$$

where I is the total intensity of selection, V is the variance of reproductive performance, and h^2 is the heritability of reproductive events.

Heritability is about 0.25 for mortality (Cavalli-Sforza and Bodmer, 1971) and about 0.10 for fertility (Henneberg, 1980). It seems that besides obvious pathologies affecting fertility, there is very little genetic variance in childbearing. Thus most of the selection occurs through differential mortality.

It is difficult to assess early intrauterine mortality because miscarriages in the first couple of weeks of pregnancies often are unnoticed or unreported. It can be estimated, however, that only about one in two conceptions will end up as a developed fetus (McNair and Altman, 2012). The rates of reported miscarriages (spontaneous abortions) reach about 30% (McNair and Altman, 2012; Wilcox et al., 1988; Goldstein, 1994). Therefore, there is a lot of room for any genetic faults that affect early development to be eliminated.

Postnatally, rates of newborn and infant mortality vary a lot; about 150 years ago they could be as high as 20%. Now, in developed countries, they have been reduced to a fraction of a percent (http://www.who.int/gho/en/, accessed 15.10.15.). Mortality rates decline with age until early adulthood when they start rising slowly reaching larger values in senility (Fig. 17.1). Up until about the mid-19th century, only about half of neonates reached age 15 years, formally taken as the beginning of the reproductive life span. Mortality during the reproductive years was still

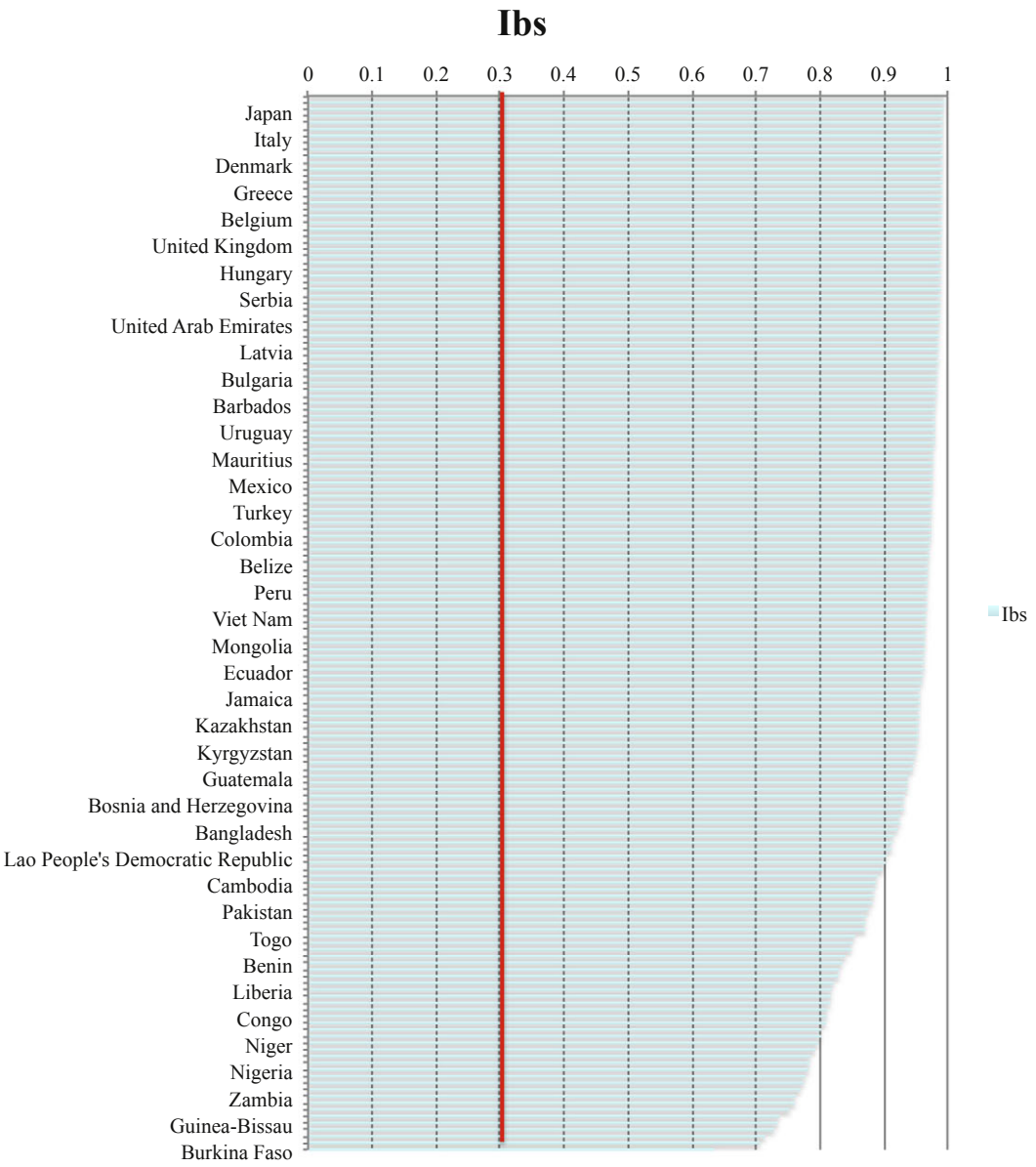

FIGURE 17.1 Values of the biological state index (I_{bs}) in all selected countries of the world in the 21st century. Own calculations based on UN and World Health Organization (WHO) data. The *red line* indicates index value characteristic for most of human history prior to the 19th century.

significant, so that only about 1/3 of those who survived to the beginning of the reproductive life span reached age 60. Such mortality provided ample opportunity for natural selection both in the prereproductive and reproductive life span. The overall opportunity for natural selection acting during postnatal lifespan can be measured using the biological state index that is a combination of amounts of age-specific mortality (d_x variable of a life table) and a degree of reproductive loss (s_x) of a person dying before completion of the reproductive life span (Henneberg, 1976; Stephan and Henneberg, 2001; Saniotis and Henneberg, 2011) (Fig. 17.1):

$$I_{bs} = 1 - \Sigma d_x s_x$$

Age-specific reproductive loss is calculated by expressing accumulated to a given age (x) annual age-specific fertility rates (f_x) as a fraction of the total fertility rate (TFR):

$$s_x = 1 - (\Sigma f_x)/\mathrm{TFR}$$

Values of s_x for subadults are obviously equal to 1, and for elderly they are zero, while within the reproductive age range they are fractions. For instance, an s_x value for a person of age 30 years can be 0.2 in a population where women delay their fertility or 0.6 where women start having children early in their lives.

Biological state index is the probability with which an individual born into a population will be able to fully participate in the reproduction of the next generation, that is, will be able to realize her fertility (Fig. 17.1). The lower this probability, the greater the opportunity for natural selection. The index does not take into account heritable variation in fertility. Considering that this variation is very low (Henneberg, 1980) the bias of the index in assessing overall opportunity for selection is small. The variance in Darwinian fitness (w) is proportional to a ratio of individuals who are reproductively unsuccessful ($1-I_{bs}$) to those who are successful (I_{bs}). High values of I_{bs} indicate a lack of opportunity for natural selection through differential mortality. Figs. 17.2 and 17.3 illustrate the difference between mortality in the premodern era and at present and the difference this produced in the opportunity for selection in various portions of human life. As can be seen in Fig. 17.2, opportunities for selection differ in various periods of individual life being the highest in early intrauterine life and early postnatal life. Changes of mortality during the last two centuries produced the greatest differences between earlier and recent selective pressures in those periods of life. Therefore, it can be expected that, in terms of body structures, mutations causing alterations in organogenesis and in differential growth of body parts can accumulate the most.

However small, heritable variation in fertility has been reduced in the last century in its possible selective impact by birth control. The negative birth control obviously does not allow natural fecundity differences to be expressed in

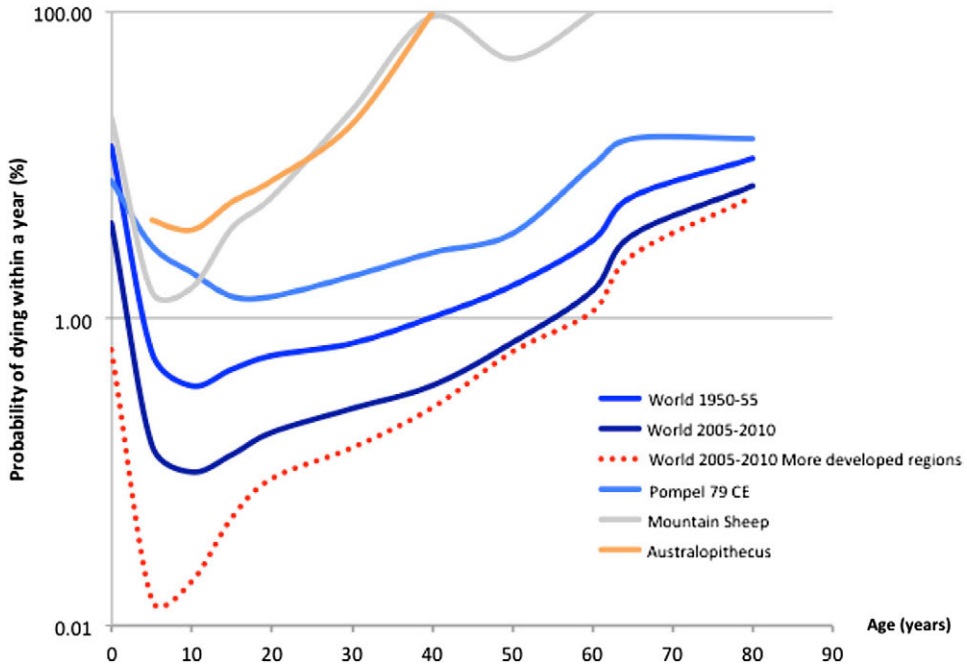

FIGURE 17.2 Postnatal mortality expressed as a probability of dying within a year (logarithmic scale) at various stages of the human biological history. Data for Australopithecine, mountain sheep (an average mammal), and humans form Pompeii (*from Saniotis, A., Henneberg, M., 2011. Medicine could be constructing human bodies in the future. Medical Hypotheses 77 (4), 560–564.*), and others (*from World Health Organization (WHO) life tables.*).

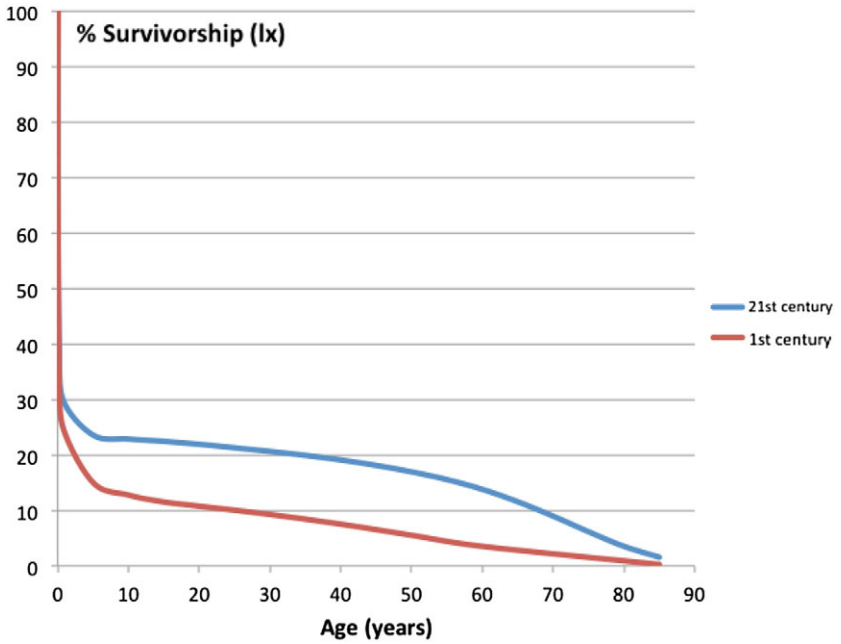

FIGURE 17.3 Survivorship from conception to a given age in the 1st century CE and in the current century. Estimations based on data from the literature on miscarriages and postnatal mortality.

different total fertility rates, while the positive birth control now allows people with limited or absent fecundity to produce offspring. Therefore, practically no genetic differences in fecundity can be reflected in differences in the number of offspring produced by parents.

Although the new situation of limited opportunity for natural selection cannot be precisely translated into actual amounts of selection acting on particular genes, it certainly lowers rates at which detrimental mutations (as per probable mutation effect) are eliminated. This in the first instance leads to increasing variation of human biological characters, but in time may lead to general deterioration of structure and function. Frequencies of alleles existing in the gene pool are subject to drift when selection is not acting. Although most populations in the modern world are large, thus limiting action of drift, drift effects will eventually become noticeable. In general, gene pools of humanity will change in the future.

GENE FLOW INCREASING VARIATION IN POPULATIONS

The gene pool of *Homo sapiens* remained linked across the entire world for at least 150,000 years to the extent that individuals from any specific population could have fertile offspring with individuals from any other population, no matter how distant. This situation has been maintained mostly by the neighborly gene exchange in which people from populations only a few kilometers apart exchange genes. Such neighbor exchanges could produce chains transporting genes over thousands of kilometers without anyone moving further than some 10–20 km during their lifetime (Brace, 2005; Henneberg, 2001a). This, although sufficient to maintain cohesion of gene pools across the world, also allowed for some differentiation through adaptations to local conditions because gene flow was slow and small. This differentiation is morphologically still visible in skin color, body form, hair form, and facial features of geographical populations. It also differentiated heritable physiological adaptations, like lactose intolerance, hemoglobinopathies related to malaria (thalassemia, sickle cell anemia), and ABO blood group frequencies.

With the development of technologies supporting long-distance travel that started, eg, in Europe in Classical Antiquity, gene flow over a few thousand kilometers could happen in the lifetime of one generation—suffice it to mention annual trade expeditions of the Romans to the Malabar Coast of India and to Nigeria. About 1000 years ago Vikings, after settling Greenland, established settlements in North America. Arabs were at that time trading with Southern Africa, their trade penetrating along rivers far inland, eg, to Mapungubwe on the Limpopo River and slightly later to the Great Zimbabwe. From the time of long-distance expeditions of Portuguese and Spanish sailors in the 15th century, genes could flow across the Atlantic and from Western Europe to the Far East.

The flow of genes across the world, due to intercontinental travel, has been significantly enhanced by better travel technologies as they developed from steamboats of the 19th century to the fast jets of the 21st century. Any

gene present in any population (as well as any infectious disease) can theoretically find its way to any other population in a matter of hours. The longest nonstop intercontinental flights nowadays take only 16–18 h. And yet we can still see phenotypic differences between people whose ancestors lived on various continents, even when themselves they reside in a new place. This is because cultural, religious, and linguistic barriers limit gene flow to surrounding indigenous populations. Such barriers, however, become slowly broken allowing mixing of the genes from different continents. Eventually, due to long-distance migrations, the human gene pool will become more homogenous, and individual variation will become the overwhelming portion of the total human variability. Genetic diseases, therefore, will become similarly prevalent in various countries requiring medical systems of particular countries to adapt to new patterns of diseases. For instance, heritable hemoglobinopathies may become rather common in countries not exposed to malarial infections.

COEVOLUTION OF HUMANS AND PATHOGENS

The human body can be considered to be a complex microbiome (Blaser, 2014). In a body of a healthy person there live multiple kilograms of a whole variety of organisms that cause no harm since they have adapted to the life inside the human organism, while our organism has adapted to their presence. These coadaptations probably required a period of Darwinian evolution of both the macroorganism and the microorganism. Not all microorganisms invading human body are, however, coadapted. Some, probably of newer historical association with humans, produce disturbances in normal operation of human tissues. They might become coadapted in the future, but currently these are considered to be infectious pathogens. The immune system of the human body tries to defend the organism against the infection, but does not always succeed. Those humans who, by the virtue of genetic variation, have greater immunity against such new microorganism causing pathologies have greater chance to pass their genes to the next generation. Invading pathogens adapt to survive body defenses so that in time a balance between virulence of pathogens and the immune system's ability to control infection is established. For example, it appears that during the last several 1000 years since *Mycobacterium tuberculosis* infected humans, such uneasy balance has been established. Through time skeletal signs of tuberculosis became less severe (Holloway et al., 2011), increasing body immunity through good diet, rest, and general health care allowed up to 80% of active cases to be healed (Holloway et al., 2014) so that now only about 10% of infected individuals develop active disease with pathological signs. For a long time tuberculosis has been known as the "disease of poverty." This is so because in situations of poverty the immune system is compromised by inadequate nutrition and bad living conditions. Since the introduction of antibiotics in the late 1940s, tuberculosis prevalence declined at different rates in various countries (Holloway et al., 2014) while *M. tuberculosis* underwent evolution in which drug-resistant strains started to proliferate. This is partly a result of inadequate treatment due to poor patient compliance. Complete cure requires many months of steady dosing with chemotherapeutics. In poorer populations many patients fail to comply with lengthy treatment allowing more drug-resistant bacteria to survive, proliferate, and infect other patients.

Even without poor compliance, evolution of pathogen would occur because antibiotics, by their nature of acting within live organisms, act by only minor alterations of biochemical processes in cells, so that some alterations of those processes by mutations are sufficient to obviate the action of the antibiotic. Since mutations are frequent and bacteria reproduce profusely and fast, the probability of the drug-insensitive mutation occurring at random is high enough to be nearly certain. Appearance of drug-resistant strains of *Treponema pallidum* causing syphilis is another example of such evolutionary change.

Use of antibiotics also has consequences for ecosystems of microbes well adapted to the life within human bodies. Such microbial communities like gut microbiota become disrupted and destabilized by the use of antibiotics to the extent of altering food digestion and absorption (Million et al., 2013). This has been used for over 50 years to increase size of domesticated animals, but also has an effect on humans.

Human microbiota, well adapted to our organisms, are subject to changes not only from the use of antibiotics, but also general alterations of the lifestyle (Tito et al., 2012). Since microbiota and human organisms are coadapted, any changes in the composition of microbiota may impact on adaptations of our bodies. Although such adaptations are likely to be primarily of immunological and physiological nature, it may be suggested that some of their effects will be reflected in bodily structures. The described trends of body size may reflect in part changing coadaptations to microorganisms living in our bodies.

ADAPTATIONS AT THE END OF LIFE

Switzerland is most famous for its liberal legislation for assisted suicide of adult patients. The organization called "Exit" (http://www.exit.ch/startseite/, accessed 21.07.15.) allows people—under certain restrictions such as being a moribund patient—to actively kill themselves, eg, in the presence of relatives. This legal framework results in a notable assisted-suicide-tourism showing the apparent

desire for such an option. Independent of individual religious and other opinions this option acts on human survivorship and shows the degree to which human medical technology and social acceptance can interfere with human survivorship, life expectancy, and so forth. More importantly it shows to what degree medical knowledge and social perception at this end of life are influencing our perspective on survivorship and life at a particular stage being worth living.

For the first time in history, human life is not considered the value to be protected at all costs. It indicates that the main aim of the medical profession is to make human life comfortable, not just prolong it. With the understanding of the evolutionary context of human biological existence it will be possible to formulate better criteria of comfortable life and apply them in practice. In terms of the mechanisms of evolution, medically assisted end of life is important only insofar as it influences reproductive performance of individuals concerned. In most cases, patients are of post-reproductive age. In those situations when the end of life comes early, it is now possible to preserve gametes for the future use in assisted reproduction procedures and thus give a patient a chance of reproducing her/his genes.

MISCARRIAGE RATE AND MATERNAL AGE AS INFLUENCING FACTORS

At the other end of human lifespan intrauterine development might be influenced by intentional and nonintentional measures. The rate of miscarriages depends on gestational age—mostly occurring before the first 7–8 weeks—as well as on mother's age. Mother's average age in industrialized countries increased enormously in the last few years. The positive effect of increased education in females in general as well as general changes in human society in the last few decades led to an increased age at first pregnancy. This again results in higher risk of miscarriage and chromosomal defects (Romero et al., 2015). Miscarriages are correlated with previous cases of miscarriages, thus in future, older women will be more likely to have repetitive miscarriages. To what extent these "natural abortions"—besides intentional termination of embryonic and fetal life—will affect the gene pool remains uncertain. Whether age alone influences the type of individual being miscarried is unclear. Human intervention, however, even indirectly as a side effect, influences this rate of survivorship at the beginning of human life. This comes on top of the fact that elder women (as well as older men to a certain extent) show decreased fertility—possibly related to decreased coital frequency (Henneberg, 1977) again influencing demographics in general. Comparison of birth intervals between dates of wedding and of the birth of the first child after the wedding for young women marrying the first time and for widows who remarried at a much older age indicates that it was duration of marriage rather than age that determined birth spacing (Table 17.2). In addition, the precise timing of conception seems to influence miscarriage rates in women with a miscarriage history (Gray et al., 1995). Taking this into account, social changes in human behavior as seen in older age of first pregnancies act indirectly onto a high degree of "selection" influencing human morphology and genetics.

TABLE 17.2 Length of the Intervals Between the Day of Wedding and the Day the First Child (all data in years) of the Couple Was Born (Protogenetic Intervals) by Women Marrying for the First Time and for the Second Time in Rural 19th Century Poland

	First Marriage ($N = 192$)		Second Marriage ($N = 42$)	
	Birth Interval	Age	Birth Interval	Age
Mean	1.9	23.0	1.6	36.6
Stdev	1.3	4.4	1.1	13.0

Note the difference in the age at marriage; all data in years.
Data from Henneberg, M., 1977. Biological dynamics of a Polish rural community in the 19th century. II System of mating and fertility. Przeglad Antropologiczny 43, 245–247, recalculated.

INFLUENCE BY IN VITRO FERTILIZATION

Evolution of technological possibilities allowing various degrees of "nonnatural" reproductive practices can influence human health and disease in the future. It is already possible to freeze gametes (both male and female) for a long time (even after the death of one partner). Major companies even support this (http://www.nbcnews.com/news/us-news/perk-facebook-apple-now-pay-women-freeze-eggs-n225011, accessed 15.10.15.) to allow especially females to better decide at which part of their lives they want to reproduce, mostly independently of natural restrictions. There will be thus in future an increased discrepancy between biological age of parents (which influences their behavior and physical fitness) and age of the gametes, and eventually offspring. This may have positive and negative effects; certain diseases such as autism (Sandin et al., 2016) are more frequent when parents are older, whereas other studies show that children of old couples are of different intelligence (Malsaspina et al., 2005). Thus again, ongoing evolution of medical technologies and social perception of what is being "normal" will directly affect human disease and health in the future; independent of the fact whether in vitro fertilization (IVF) itself means a higher risk of birth defects and other risk to the offspring as discussed extensively and contradictorily. With IVF technologies it

is possible for individuals, or couples, who were previously infertile, to have offspring. If these individuals had genetic defects causing infecundity, these defects can be passed to their IVF-produced offspring.

INFLUENCES OF CHANGES IN FAMILY STRUCTURE

Surrogate motherhood is becoming a common phenomenon. Embryonic and fetal development is determined by an interaction between genetic regulation of growth and the effects of maternal intrauterine environment that influences epigenetic phenomena. Obviously, implanting an embryo produced by the union of two gametes of specific individuals in the uterus of a third person will lead to the development of a fetus different from the one that would have developed in the womb of its genetic mother. A phenotype of a child will be altered. These alterations may be for the better; the fact, however, remains that three persons, rather than two, will have an input.

Collective parenting, which was an important factor in the past, is increasingly disappearing in modern Western societies. Various factors such as migration of relatives, separation, and increased workload, lead to less related people being responsible for someone's parenting. Due to changes in the social role of marriages, greater divorce rates, gender equity, and professionalism of women, single motherhood (and also to a certain extent increasingly single fatherhood) is a common recent phenomenon. Although this is unlikely to have direct genetic consequences, it may alter the ontogeny and social maturation of children that will have behavioral consequences for future mating practices. With these phenomena the number of adults a child has closer relations with is very limited, and advice to mothers regarding the needs of a growing child may be limited to what is generally available from health authorities with less personalized input of older relatives. With increasing mobility of individuals, when children grow up there is a greater chance they will find partners outside of their own cultural groups. Besides increasing gene flow, it may lead to differences in the views on child rearing in the next generation that can influence their physical development. One simple example is diet; vegetarians have less of a chance to develop obesity (Grantham et al., 2014).

CHANGES IN HEALTH AND DISEASE DEFINITION AS A CONSEQUENCE

All the alterations of human body morphology and genetics listed earlier as well as the environment, including social perception, lead to a change in human health and disease definitions.

Categorization of human disease is fundamental in medicine. Common ways doing so are, eg, the World Health Organization (WHO) international categorization of disease (http://www.who.int/classifications/icd/en/, accessed 15.10.15.). This system is used to categorize and explain the main etiology of a disease or a syndrome, and for statistical and billing purposes. It is a well-established system of categorization. However, with changes in understanding disease processes (including new genetic information) and with improved evolutionary explanations, one should consider a novel way to classify disease. This has been proposed by Stearns and Medzithov (2016) who suggested a very elaborate framework of novel disease classification, which would use more fundamental causes as criteria.

Disease etiology (underlying factors) is changing as well as definitions of disease or health itself. Defining disease is actually different from defining health. Using WHO definition of health—"Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (Preamble of the WHO, 1946)—one can address the following.

Taking the processes of ongoing evolution discussed in this chapter into account, one can assume that particular mental and social well-being as a proxy for health is even more fluctuating/flexible than disease itself. One such example would be smoking. Widely regarded as socially acceptable in the mid-20th century even for pregnant women, nowadays—for obvious, good medical reasons—smoking is heavily banned, and thus a heavy smoker may not feel social well-being and will not be healthy based on the WHO definition, independent of whether or not the smoker's habit makes him or her physically sick, such as from lung carcinoma or chronic coughing. Homosexuality in the past had been regarded as a disease; now, in most Western countries it has been completely legalized and is regarded as a normal variation of sexual orientation. Other examples include personal use of cannabis and other drugs used in indigenous populations but not allowed in certain Western societies. The global outreach and broad definition of the WHO health approach and medical disease classification thus can serve as an indicator of how frameworks on health and disease in general, both in social and medical environment, depend on zeitgeist rather than only on strict disease classification. Some classifications of disease may, due to ongoing evolution, disappear in the future mostly or completely. Preimplantation diagnostics (eg, just recently approved by Swiss voters in 2015) may eradicate completely those major genetic diseases that are diagnosable and congenital malformations. On the other hand, with improvements of medical diagnostics, a couple deciding to carry out a baby with major genetic defects will be regarded by the society as abnormal because they do not use the possibility of abortion in such a case, and thus it will not feel healthy because of social stigmatization, independent of the fact that they are

physically healthy. The introduction of iodized salt in Switzerland (Papageorgopoulou et al., 2012), a classic example of a public health measure, lead to the nearly complete disappearance of cretinism in these regions. Other major impact diseases such as smallpox or HIV—by human intervention or behavior—appear and disappear in short periods.

A new framework of disease classification that takes evolutionary rather than pure single-factored, mechanistic criteria into account would be more up to date and take the issues raised earlier into account. In the future human disease definitions will be even more fluctuating and thus more complex; by adding an evolutionary perspective at least part of this challenge could be overcome.

To summarize, disease (and health) classifications and relevance will be adjusted, eg, due to the ongoing changes in medical intervention (leading to the eradication of a particular condition), body morphology and genetics, evolution of pathogens, or changes in social perception. Thus evolutionary medicine, by addressing ongoing evolution of intrinsic and extrinsic factors influencing human health, can contribute to a differentiated perspective for the understanding of human nature, its major medical challenges, and future.

ACKNOWLEDGMENT

The authors would like to acknowledge the Mäxi Foundation.

REFERENCES

Betts, D.H., King, W.A., 2001. Genetic regulation of embryo death and senescence. Theriogenology 55, 171–191.

Bhatia, K., Ghabriel, M.N., Henneberg, M., 2005. Anatomical variations in the branches of the human aortic arch: a recent study of a South Australian population. Folia Morphologica (Warsz) 64 (3), 217–223.

Bielicki, T., Welon, Z., 1982. Growth data as indicators of social inequalities: the case of Poland. American Journal of Physical Anthropology 25, 153–167.

Blaser, M.J., 2014. The microbiome revolution. Journal of Clinical Investigation 124, 4162–4165.

Bogin, B., Wall, M., MacVean, R.B., 1992. Longitudinal analysis of adolescent growth of ladino and Mayan school children in Guatemala: effects of environment and sex. American Journal of Physical Anthropology 89 (4), 447–457.

Brace, C.L., 1964. The probable mutation effect. The American Naturalist 98, 453–455.

Brace, C.L., 2005. Race Is a Four Letter Word. Oxford University Press, New York.

Brace, C.L., Rosenberg, K.R., Hunt, K.D., 1987. Gradual change in human tooth size in the late pleistocene and post-pleistocene. Evolution 705–720.

Cavalli-Sforza, L.L., Bodmer, W.F., 1971. The Genetics of Human Populations. W. H. Freeman, San Francisco.

Collard, M., Wood, B., 2015. Defining the genus *Homo*. In: Henke, W., Tattersall, I. (Eds.), Handbook of Paleoanthropology. Springer-Verlag, Berlin Heidelberg.

Crow, J.F., 1958. Some possibilities for measuring selection intensities in man. Human Biology 30, 1–13.

Debetz, G.F., 1960. Certains aspects des transformations somatiques de l'Homo sapiens. In: Communiques de la Delegation Sovietique au Ve Congres International des Sciences Anthropologiques, Moscow, p. 25.

Debetz, G.F., 1964. Essai de determination du poids des hommes vivants d'apres les dimensions des os longs. In: VII^{e} Congr. Internat. Sci. Anthrop. Ethnol., vol. 11, pp. 243–250.

Goldstein, S.R., 1994. Embryonic death in early pregnancy: a new look at the first trimester. Obstetrics & Gynecology 84, 294–297.

Grantham, J.P., Staub, K., Rühli, F.J., Henneberg, M., 2014. Modern diet and metabolic variance—a recipe for disaster? Nutrition Journal 6, 13–15.

Gray, R.H., Simpson, J.L., Kambic, R.T., Queenan, J.T., Mena, P., Perez, A., Barbato, M., 1995. Timing of conception and the risk of spontaneous abortion among pregnancies occurring during the use of natural family planning. American Journal of Obstetrics & Gynecology 172, 1567–1572.

Henneberg, M., 1976. Reproductive possibilities and estimations of the biological dynamics of earlier human populations. Journal of Human Evolution 5, 41–48.

Henneberg, M., 1977. Biological dynamics of a Polish rural community in the 19th century. II System of mating and fertility. Przeglad Antropologiczny 43, 245–247.

Henneberg, M., 1980. Natural selection through differential fertility in human populations: quantitative evaluation of selection intensity. Przeglad Antropologiczny 46, 21–60.

Henneberg, M., 1988. Decrease of human skull size in the Holocene. Human Biology 395–405.

Henneberg, M., 1998. Evolution of the human brain: is bigger better? Clinical and Experimental Pharmacology and Physiology 25, 1640–1681.

Henneberg, R.J., Henneberg, M., 1999. Variation in the closure of the sacral canal in the skeletal sample from Pompeii, Italy 79 AD. Perspectives in Human Biology 4, 177–188.

Henneberg, M., 2001a. The gradual eurytopic evolution of humans: not from Africa alone. In: Indriati, E. (Ed.), Man: Past, Present, and Future. Bigraf Publishing, Yogyakarta, Indonesia, pp. 42–52.

Henneberg, M., 2001b. Secular trends in body height – indicator of general improvement in living conditions or of a change in specific factors? In: Dasgupta, P., Hauspie, R. (Eds.), Perspectives in Human Growth, Development and Maturation. Kluwer Academic Publishers, Boston, pp. 159–168.

Henneberg, M., 2006. The rate of human morphological microevolution and taxonomic diversity of hominids (Essays in memory of Andrzej Wiercinski). Studies in Historical Anthropology 4, 49–59.

Henneberg, M., Budnik, A., Pezacka, M., Puch, A.E., 1984. The mechanism of brachycephalization: differential susceptibility to infectious diseases during childhood. Przeglad Antropologiczny 50, 325–333.

Henneberg, M., George, B.J., 1995. Possible secular trend in the incidence of an anatomical variant: median artery of the forearm. American Journal of Physical Anthropology 96 (4), 329–334.

Henneberg, M., Louw, G.J., 1998. Cross-sectional survey of growth of urban and rural "cape coloured" schoolchildren: anthropometry

and functional tests. American Journal of Human Biology 10, 73−85.

Henneberg, M., van den Berg, E.R., 1990. Test of socioeconomic causation of secular trend: stature changes among favored and oppressed South Africans are parallel. American Journal of Physical Anthropology 83, 459−465.

Henneberg, M., LaVelle, M., 1999. Varying effects of socioeconomic categories on the growth of urban and rural South African 'Cape Coloured' boys. Perspectives in Human Biology 4, 41−49.

Holloway, K.L., Henneberg, R.J., de Barros Lopes, M., Henneberg, M., 2011. Evolution of human tuberculosis: a systematic review and meta-analysis of paleopathological evidence. Homo 62, 402−458.

Holloway, K.L., Staub, K., Rühli, F., Henneberg, M., 2014. Lessons from history of socioeconomic improvements: a new approach to treating multi-drug-resistant tuberculosis. Journal of Biosocial Science 46 (5), 600−620.

Imsland, F., Feng, C., Boije, H., Bed'hom, B., Fillon, V., Dorshorst, B., Rubin, C.J., Liu, R., Gao, Y., Gu, X., Wang, Y., Gurichon, D., Zody, M.C., Zecchin, W., Vieaud, A., Tixier-Boichard, M., Hu, X., Hallbook, F., Li, N., Andersson, L., 2012. The Rose-comb mutation in chickens constitutes a structural rearrangement causing both altered comb morphology and defective sperm motility. PLoS Genetics 8 (6).

Jumea, F., Com, E., Lane, L., Duek, P., Lagarrigue, M., Lavigne, R., Guillot, L., Rondel, K., Gateau, A., Melaine, N., Guével, B., Sergeant, N., Mitchell, V., Pineau, C., 2015. Human spermatozoa as a model for detecting missing proteins in the context of the chromosome-centric human proteome project. Journal of Proteome Research 14, 3606−3620.

Kaidonis, J., Townsend, G., 2016. The 'sialo−microbial−dental complex' in oral health and disease. Annals of Anatomy − Anatomischer Anzeiger (in press).

Komlos, J. (Ed.), 1994. Stature, Living Standards, and Economic Development. The University of Chicago Press, Chicago.

Lee, Y.C., Solomon, L.B., Rühli, F.J., Schiess, R., Öhrström, L., Sullivan, T., Alkadhi, H., Henneberg, M., 2011. Confirmation of microevolutionary increase in spina bifida occulta among Swiss birth cohorts. European Spine Journal 20 (5), 776−780.

Lockhart, P.B., Bolger, A.F., Papapanou, P.N., Osinbowale, O., Trevisan, M., Levison, M.E., Taubert, K.A., Newburger, J.W., Gornik, H.L., Gewitz, M.H., Wilson, W.R., Smith Jr., S.C., Baddour, L.M., American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, Council on Clinical Cardiology, 2012. Periodontal disease and atherosclerotic vascular disease: does the evidence support an independent association? Circulation 125, 2520−2544.

Malaspina, D., Reichenberg, A., Weiser, M., Fenning, S., Davidosn, M., Hartap, S., Wolitzky, R., Rabinowitz, J., Susser, E., Knoberl, H.Y., 2005. Paternal age and intelligence: implications for age-related genomic changes in male germ cells. Psychiatric Genetics 16, 117−125.

McNair, T., Altman, K., 2012. Miscarriage and recurrent pregnancy loss. In: Joseph Hurt, K., Guile, M.W., Bienstock, J.L., Fox, H.E., Wallach, E.E. (Eds.), The Johns Hopkins University School of Medicine Department of Gynecology and Obstetrics. Lippincott Williams & Wilkins.

Meek, R.W., Hrushi, V., Piddock, L.J.V., 2015. Nonmedical uses of antibiotics: time to restrict their use? PLoS Biology 13 (10), e1002266.

Million, M., Thuny, F., Angelakis, E., Casalta, J.P., Giorgi, R., Habib, G., Raoult, D., 2013. Lactobacillus reuteri and *Escherichia coli* in the human gut microbiota may predict weight gain associated with vancomycin treatment. Nutrition & Diabetes 9 (3), e87.

Moishezon-Blank, N., 1991. Commentary oft he possible effect of hormones in food on human growth. Medical Hypotheses 38, 273−277.

Papageorgopoulou, C., Rühli, F., Staub, K., 2012. Hypothyreoidism in Switzerland. In: Harbeck, M., von Heyking, K., Schwarzberg, H. (Eds.), Sickness, Hunger, War, and Religion in: Multidisciplinary Perspectives (vol. 1, p. 3). RCC Perspect.

Preamble to the Constitution of the World Health Organization as Adopted by the International Health Conference, New York, 19−22 June, 1946 signed on 22 July 1946 by the representatives of 61 States (Official Records of the World Health Organization, no. 2, p. 100) and entered into force on 7 April 1948.

Romero, S.T., Geiersbach, K.B., Paxton, C.N., Rose, N.C., Schisterman, E.F., Branch, D.W., Silver, R.M., 2015. Differentiation of genetic abnormalities in early pregnancy loss. Ultrasound in Obstetrics & Gynecology 45 (1), 89−94.

Sandin, S., Schendel, D., Magnusson, P., Hultman, C., Surén, P., Susser, E., Grønborg, T., Gissler, M., Gunnes, N., Gross, R., Henning, M., Bresnahan, M., Sourander, A., Hornig, M., Carter, K., Francis, R., Parner, E., Leonard, H., Rosanoff, M., Stoltenberg, C., Reichenberg, A., 2016. Autism risk associated with parental age and with increasing difference in age between the parents. Molecular Psychiatry (in press).

Saniotis, A., Henneberg, M., 2011. Medicine could be constructing human bodies in the future. Medical Hypotheses 77 (4), 560−564.

Satyapal, K.S., 2003. The renal veins: a review. European Journal of Anatomy Suppl. 1, 43−52.

Satyapal, K.S., Haffejee, A.A., Singh, B., Ramsaroop, L., Robbs, J.V., Kalideen, J.M., 2000. Additional renal arteries: incidence and morphometry. Surgical and Radiologic Anatomy 23, 33−38.

Scott, G.R., Irish, J.D., 2013. Anthropological Perspectives on Tooth Morphology: Genetics, Evolution, Variation. Cambridge University Press, Cambridge.

Schwidetzky, I., 1962. Das grazilisierungs problem. Homo 13 (3), 188−195.

Shea, B.T., 1989. Heterochrony in human evolution: the case for neoteny reconsidered. Yearbook of Physical Anthropology 32, 69−101.

Solomon, L.B., Rühli, F.J., Taylor, J., Ferris, L., Pope, R., Henneberg, M., 2003. A dissection and computer tomograph study of tarsal coalitions in 100 cadaver feet. Journal of Orthopaedic Research 21 (2), 352−358.

Solomon, B., Rühli, F.J., Lee, Y.C., Henneberg, M., 2009. Secular trend in the opening of the sacral canal: an Australian study. Spine 34 (3), 244−248.

Staub, K., Rühli, F.J., 2013. From growth in height to growth in breadth: the changing body shape of Swiss conscripts since the late 19th century and possible endocrine explanations. General and Comparative Endocrinology 1 (188), 9−15.

Stearns, S., Medzhitov, R., 2016. Evolutionary Medicine. Sinauer.

Stephan, C.N., Henneberg, M., 2001. Medicine may be reducing the human capacity to survive. Medical Hypotheses 57 (5), 633−637.

Strzałko, J., Henneberg, M., Piontek, J., 1980. In: Human Populations as Biological Systems, a Monograph. Polish Scientific, Warsaw.

Tito, R.Y., Knights, D., Metcalf, J., Obregon-Tito, A.J., Cleeland, L., Najar, F., Roe, B., Reinhard, K., Sobolik, K., Belknap, S., Foster, M., Spicer, P., Knight, R., Lewis Jr., C.M., 2012. Insights from characterizing extinct human gut microbiomes. PLoS One 7 (12), e51146.

Ulijaszek, S.J., Henneberg, M., 2012. Results of epidemiological studies of blood pressure are biased by continuous variation in arm size related to body mass. Human Biology, 437–444.

Van Wierigen, J.C., 1986. Secular growth changes. In: Falkner, F., Tanner, J.M. (Eds.), Human Growth. A Comprehensive Treatise. Methodology, Ecological, Genetic and Nutritional Effects on Growth. Plenum, New York, pp. 307–331.

Warinner, C., Hendy, J., Speller, C., Cappellini, E., Fischer, R., Trachsel, C., Arneborg, J., Lynnerup, N., Craig, O.E., Swallow, D.M., Fotakis, A., Christensen, R.J., Olsen, J., Liebert, A., Montalva, N., Fiddyment, S., Mackie, M., Bouwman, A., Rühli, F., Gilbert, M.T.P., Collins, M.J., 2014. Direct evidence of milk consumption from ancient human dental calculus. Scientific Reports 27 (4), 7104.

Wilcox, A.J., Weinberg, C.R., O'Connor, J.F., Baird, D.D., Schlatterer, J.P., Canfield, R.E., Armstrong, E.G., Nisula, B.C., 1988. Incidence of early loss of pregnancy. The New England Journal of Medicine 319, 189–194.

Part II

Psychology, Behavior and Society

Chapter 18

Gene-Culture Models for the Evolution of Altruistic Teaching

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Universities are places of learning rather than teaching.

Murray Gell-Mann, at the Santa Fe Institute, 1985

INTRODUCTION

Models with Genetic and Cultural Transmission

In classical quantitative genetics, the phenotype of an offspring is regarded as the sum of components due to the offspring's genotype, the offspring's environment, and possible interactions between these. The offspring's genotype is, of course, a function of its parents' genotypes. Its environment, however, could be interpreted as random and/or peculiar to that offspring or as some properties of its parents, and transmission of these properties involves teaching, learning, and some combination of these.

In the first model of dual cultural and genetic inheritance, Cavalli-Sforza and Feldman (1973) expressed the phenotype of an offspring of genotype g whose parent had mean phenotype ϕ_m as ϕ_{gm}, where

$$\phi_{gm} = a_g + 2b_g\phi_m + \varepsilon, \tag{18.1}$$

where ε is a random variable, a_g is a contribution to the offspring's phenotype by its genotype g, and b_g measures the contribution to the phenotype of an offspring of genotype g due to its parents' phenotypes. Thus ϕ_{gm} can be termed the "phenogenotype" of this offspring.[1] The variation in this framework was regarded as continuous. The model specified by Eq. (18.1) allows allele frequencies to remain constant, and these frequencies contribute to the dynamics of phenotypic variation; at phenotypic equilibrium, correlations between relatives can be computed and depend on these allele frequencies. Note that since g is a property of the offspring here, parental genotypes do not directly influence the transmission of their phenotypes.

For discrete valued traits, the earliest models of cultural transmission and evolution (Cavalli-Sforza and Feldman, 1981) posited a dichotomous trait with types 1 and 2. Under purely vertical transmission, each of the four biparental pairs is associated with a probability that their offspring is of type 1. These probabilities, b_3, b_2, b_1, b_0, for parental pairs (1,1), (1,2), (2,1), (2,2), respectively, define the vertical cultural transmission and determine the evolution of the frequency of type 1 in the population. The transmission rates b_i confound teaching by parents and learning by their offspring and do not involve any biological contribution to the transmission process.

Besides vertical transmission described by the b_i, the probability that an individual acquires type 1 might depend on that individual contacting peers or nonparental members of the parental generation. In these cases, horizontal and oblique transmission, respectively, transmission of type 1 depends on its frequency in the respective generations (Cavalli-Sforza and Feldman, 1981) and can be regarded as a consequence of social interactions. Again, genetic properties of the participants are not included in the rules of transmission.

A simple and direct way to introduce genetics into the transmission of a dichotomous cultural trait was proposed by Feldman and Cavalli-Sforza (1976). They considered phenogenotypes to be a combination of a dichotomous trait with phenotypes 1 and 2 and genotypes at single biallelic

1. To the authors' knowledge, the first use of the term "phenogenotype," signaling dual inheritance, is in Uyenoyama et al. (1979).

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00018-1

locus: AA_1, AA_2, Aa_1, Aa_2, aa_1, aa_2. (Phenotype here is equivalent to the corresponding variant of the dichotomous trait.) There are then 36 possible parental couples, and one member of the couple is designated as "the teacher." If the teaching parent has phenotype 1, then the probabilities that offspring of genotypes AA, Aa, and aa are also of phenotype 1 can be written b_1, b_2, b_3, respectively, while if the teaching parent is of type 2 these probabilities are c_1, c_2, c_3, respectively. This phenogenotypic transmission scheme explicitly posits that the offspring's genotype and the teaching parent's phenotype determine the rate of transmission. Again, the "teacher's" genotype does not appear. Feldman and Cavalli-Sforza went on to explore the interaction between these phenogenotypic transmission rates and direct selection on the phenotypic dichotomy of the offspring. A different version of this framework, without the specific introduction of the teacher's phenotype and ignoring fitness differentials among phenotypes, but with contributions from the offspring's genotype and the parental couples' phenotypes, was analyzed in Feldman et al. (2013), where the focus once again was on correlations between relatives.

Social Learning and Altruistic Teaching

All of the models described above involve some form of social learning, whether the social derives from parents, peers, or other subgroups in the population. Social learning is a generic term for the acquisition of knowledge or a behavior or a skill from another individual, eg, by local enhancement, imitation, etc. It is usually contrasted with individual learning, which occurs without input from other individual(s); that is without social interaction, eg, by trial and error. Teaching is a special case of social learning in which the other individual(s) actively participate(s) in the information transfer. The transmission models described above do not include any costs to offspring of the cognitive machinery that allows them to learn or of the machinery that allows parents to teach.

There is a vigorous debate on how to define and identify teaching in nonhuman animals, and indeed also in humans (eg, Caro and Hauser, 1992; Hoppitt et al., 2008; Byrne and Rapaport, 2011; Hewlett et al., 2011). Using an operational definition (see later in this chapter), Caro and Hauser (1992; see also Hoppitt et al., 2008) review the possible examples of teaching in nonhuman animals. In these putative cases, which occur among diverse taxonomic orders and often involve parents teaching their offspring, the teacher(s) could be one parent, usually the mother, or both parents. Interestingly, teaching is at best extremely rare in our closest biological relative, the chimpanzee.

In its barest essentials, the operational definition of teaching from Caro and Hauser (1992; see also Fogarty et al., 2011) entails that a knowledgeable individual (the "teacher") alters its behavior in the presence of a naïve individual (the "pupil"), incurring a cost to do so, and thereby promotes social learning by that naïve individual. The cognitive processes that support teaching, given that it occurs, are likely to differ across the taxonomic orders (Hoppitt et al., 2008). Hence, the comparative approach, based on this operational definition, may not be "helpful in understanding the evolution of the distinctively human attributes" of teaching (Byrne and Rapaport, 2011). Nevertheless, this operational definition provides a useful framework for modeling the evolution of teaching, because mathematical models addressing the evolution of a behavior are usually formulated in terms of who does what to whom with what costs and benefits, rather than in terms of intentions and motivations. If teaching entails a fitness cost to the teacher and a fitness benefit to the pupil, then it can be regarded as an altruistic act (Aoki and Feldman, 1987; Hoppitt et al., 2008).

Competition Between Teachers and Nonteachers

Fogarty et al. (2011) modeled the competition between two genetically determined types, teacher and nonteacher, in a species where social learning is already in place (Wakano et al., 2004; Aoki et al., 2005; Wakano and Aoki, 2006). They assume that a naïve individual is more likely to acquire beneficial information by social learning when its exemplar is a teacher than a nonteacher. Moreover, they introduce two costs, a fixed cognitive cost that is incurred by all teachers and is associated with the neural substrate for teaching, and a behavioral cost due to the act of teaching that affects only teachers carrying the beneficial information. Their model permits arbitrary degrees of relatedness between the teacher and the pupil, which entails an *approximation*. The inclusive fitness benefit that results from the relatives of a teacher being more likely than the relatives of a nonteacher to acquire the beneficial information is found to be a crucial factor governing the evolution of teaching.

More specifically, Fogarty et al. (2011) define the fitness of teachers as

$$W_t = P(l|t)w_0w_ic_t + (1 - P(l|t))w_0 - c_c, \qquad (18.2)$$

where $P(l|t)$ is the probability that a teacher acquires the beneficial information, w_0 is the baseline fitness, w_i is relative viability of an individual with the beneficial information, c_c is the cognitive cost to teachers, and c_t represents the cost of the teaching act. Similarly, the fitness of nonteachers is defined as

$$W_{nt} = P(l|nt)w_0w_i + (1 - P(l|nt))w_0, \qquad (18.3)$$

where $P(l|nt)$ is the probability that a nonteacher acquires the beneficial information. Then, a two-timescale approach is apparently used to derive the one-dimensional dynamical equation

$$t' = \frac{tW_t}{tW_t + (1-t)W_{nt}} \tag{18.4}$$

describing the change in the frequency of teachers, t, per generation. Eqs. (18.2)–(18.4) correspond to Eqs. (2a), (2b), and (6), respectively, of their paper. Fogarty et al. (2011) conclude that there are no internal equilibria of Eq. (18.3). That is, teachers and nonteachers cannot coexist at equilibrium, and teachers will replace nonteachers if they are able to invade.

Background for the New Model

In this chapter, we adopt many of the assumptions made by Fogarty et al. (2011), but we focus on one particular but important type of kin relationship, namely parent–child, and formulate coevolutionary dynamical models in the frequencies of the four phenogenotypes, namely, teacher and nonteacher with and without the beneficial information. Empirical surveys of teaching in nonhuman animals mentioned earlier suggest that in a significant fraction of the possible examples parents teach their offspring. This is understandable in the light of inclusive fitness theory (Hamilton, 1964), since parents are closely related to their offspring, and the benefit accruing to the offspring is expected to be large relative to the cost suffered by the parent(s). Hence, the parent–child relationship is arguably the most important setting in which the evolution of teaching would occur. Our analyses of the stability of fixation states suggest that internal equilibria, stable and unstable, may be the rule rather than the exception. Such dynamics are usually not captured by the standard inclusive fitness arguments such as have been employed by Fogarty et al. (2011; see Cavalli-Sforza and Feldman, 1978 and Uyenoyama and Feldman, 1981).

We are particularly interested in the balance of selective forces that resulted in the emergence of teaching in hominids. There is evidence suggesting that teaching of stone-tool production skills occurred during the Upper Paleolithic. Archaeological studies of refitted lithic materials from sites in Europe and Japan suggest that expert knappers may have taught such skills to novices. For example, good blades were apparently produced not for immediate use but so that novices could observe the operational sequence (Takakura, 2013 and references therein).

If teaching evolved in hominids after the separation from the chimpanzee lineage, then it would have been in the context of a hunter-gatherer life history. Anthropological research on present-day hunter-gatherers (Hewlett et al., 2011; Hewlett, 2013) suggests a developmental change in social learning from a reliance on vertical transmission (learning from parents) to oblique (learning from other members of the parental generation) and/or horizontal transmission (learning from members of the same generation). Hence, we also consider the effects of incorporating oblique or horizontal transmission, which can occur between nonkin and might be expected to disfavor the evolution of teaching. In addition, temporal environmental variability should not be neglected, as theoretical work has repeatedly demonstrated its important role in the evolution of learning in general (eg, Boyd and Richerson, 1985; Rogers, 1988; Feldman et al., 1996).

BASIC HAPLOID MODEL WITH ASEXUAL REPRODUCTION AND UNIPARENTAL TRANSMISSION (ARUT)

We now introduce a minimal model for the evolution of teaching that incorporates the basic factors in their simplest form. These factors include two different costs to teaching (Fogarty et al., 2011), vertical (parent–child) transmission of an adaptive phenotype (Creanza et al., 2013), and environmental change. The explicit results derived from a full analysis of this model provide a baseline against which the effects of introducing more realistic assumptions—sexual reproduction with biparental transmission, oblique/horizontal transmission—can be compared.

Model Description

The model to be described here posits asexual reproduction and uniparental transmission (ARUT).

Assume an infinite population of haploid individuals that have discrete generations, reproduce asexually, and are capable of social learning. A genetic locus with two alleles, A and a, determines whether an individual is a teacher or a nonteacher, respectively. Each individual is also distinguished by its dichotomous phenotype, which, instead of type 1 and 2 used earlier, we represent as bar and not-bar. Bar is the phenotype that is expressed when the individual acquires beneficial information by cultural transmission. There are four phenogenotypes (phenotype–genotype combinations): bar teachers, not-bar teachers, bar nonteachers, and not-bar nonteachers. We write $\overline{x}$, x, $\overline{y}$, and y, respectively, for the frequencies of $\overline{A}$, A, $\overline{a}$, a among reproductive adults, where $\overline{x} + x + \overline{y} + y = 1$.

In the ARUT model, a newborn can only acquire the bar phenotype from its only parent. All individuals can learn socially, but having a teacher as the parent increases the efficiency of social learning. Let the vertical transmission rates from bar teachers and bar nonteachers be α and β, respectively, where $0 < \beta < \alpha < 1$. Offspring

of a not-bar parent are necessarily not-bar. Both transmission parameters include the effect of information decay. That is, each is smaller than the transmission fidelity that could be achieved in a constant environment, because beneficial information may become obsolete due to environmental change (eg, Kendal et al., 2009; Lehmann and Feldman, 2009). This is one of several ways of modeling the effect of environmental change on social learning (Aoki and Feldman, 2014). In addition, there is a cost to the teaching act, such that bar teachers $(\overline{A})$ have lower relative fertility, $1-\delta$, where $\delta > 0$ (Creanza el al., 2013). Not-bar teachers (A) do not teach and hence do not suffer this cost.

From these assumptions, it follows that the frequencies of the four phenogenotypes among the newborns of the next generation after vertical transmission, $\overline{x}_v$, x_v, $\overline{y}_v$, y_v, satisfy

$$V\overline{x}_v = (1-\delta)\overline{x}\alpha \tag{18.5}$$

$$Vx_v = (1-\delta)\overline{x}(1-\alpha) + x \tag{18.6}$$

$$V\overline{y}_v = \overline{y}\beta \tag{18.7}$$

$$Vy_v = \overline{y}(1-\beta) + y \tag{18.8}$$

where

$$V = 1 - \delta\overline{x}. \tag{18.9}$$

For example, the first term on the right-hand side of Eq. (18.6) gives the offspring of $\overline{A}$ that are unable to acquire the bar phenotype from their parents, which occurs with probability $1-\alpha$. The frequency of these offspring is further reduced by a factor $1-\delta$, because of the fertility cost incurred by their parents associated with teaching. Similarly, the second term gives the offspring of A, who will necessarily be not-bar.

After vertical transmission, selection occurs during maturation such that teachers have lower relative viability, $1-\gamma$, due to the developmental cost of the neural substrate for teaching ($\gamma > 0$), whereas the bar phenotype confers a higher relative viability, $1+s$, because the transmitted information is beneficial ($s > 0$). Hence, assuming multiplicative viability effects, the frequencies of the four phenogenotypes among the reproductive adults of the next generation are

$$W\overline{x}' = (1-\gamma)(1+s)\overline{x}_v \tag{18.10}$$

$$Wx' = (1-\gamma)x_v \tag{18.11}$$

$$W\overline{y}' = (1+s)\overline{y}_v \tag{18.12}$$

$$Wy' = y_v \tag{18.13}$$

where

$$W = (1-\gamma)(1+s)\overline{x}_v + (1-\gamma)x_v + (1+s)\overline{y}_v + y_v. \tag{18.14}$$

Here and elsewhere, a prime indicates that the variable is evaluated in the next generation.

Global Properties of ARUT Model

On substituting Eqs. (18.5)–(18.9) into Eqs. (18.10)–(18.14), we obtain

$$\begin{pmatrix} \overline{x}' \\ x' \\ \overline{y}' \\ y' \end{pmatrix} = (WV)^{-1} \begin{pmatrix} (1-\gamma)(1-\delta)(1+s)\alpha & 0 & 0 & 0 \\ (1-\gamma)(1-\delta)(1-\alpha) & 1-\gamma & 0 & 0 \\ 0 & 0 & (1+s)\beta & 0 \\ 0 & 0 & 1-\beta & 1 \end{pmatrix} \begin{pmatrix} \overline{x} \\ x \\ \overline{y} \\ y \end{pmatrix}. \tag{18.15}$$

Eq. (18.15) is linear in the four variables, $\overline{x}$, x, $\overline{y}$, and y, except for the scalar normalizing factor $(WV)^{-1}$, which is the inverse of the mean fitness. Inspection of Eq. (18.15) reveals that it has four kinds of equilibria. One of these, fixation on A, teaching-not-bar, cannot be stable because $\gamma > 0$. Further analysis of the recursion system is given in Appendix 1 and can be summarized as follows. Teaching evolves if

$$(1+s)\beta < 1 \quad \text{and} \quad (1-\gamma)(1-\delta)(1+s)\alpha > 1, \tag{18.16}$$

or

$$(1+s)\beta > 1 \quad \text{and} \quad (1-\gamma)(1-\delta)(1+s)\alpha > (1+s)\beta. \tag{18.17}$$

As shown in Appendix 1, the following are the equilibria and their stability conditions. Carets denote equilibrium values.

Fixation of Nonteachers with Nonadaptive Phenotype

Here

$$(\widehat{\overline{x}}, \widehat{x}, \widehat{\overline{y}}, \widehat{y}) = (0,0,0,1), \tag{18.18}$$

and only a is present. This equilibrium always exists and is stable if $(1+s)\beta < 1$.

Fixation of Nonteachers, Polymorphism of Adaptive and Nonadaptive Phenotypes

Here, only $\overline{a}$ and a are present:

$$(\widehat{\overline{x}}, \widehat{x}, \widehat{\overline{y}}, \widehat{y}) = \left(0, 0, \frac{(1+s)\beta - 1}{s\beta}, \frac{1-\beta}{s\beta}\right). \quad (18.19)$$

This equilibrium exists if and only if $(1+s)\beta > 1$. When it exists it is stable if $(1-\gamma)(1-\delta)(1+s)\alpha < (1+s)\beta$. This condition ensures that teachers cannot invade and replace nonteachers.

Fixation of Teachers, Polymorphism of Adaptive and Nonadaptive Phenotypes

Here, only $\overline{A}$ and A are present:

$$(\widehat{\overline{x}}, \widehat{x}, \widehat{\overline{y}}, \widehat{y}) = \left(\frac{(1-\delta)(1+s)\alpha - 1}{(1-\delta)(1+s\alpha) - 1}, \frac{(1-\delta)(1-\alpha)}{(1-\delta)(1+s\alpha) - 1}, 0, 0\right), \quad (18.20)$$

which exists if and only if $(1-\delta)(1+s)\alpha > 1$. When it exists it is stable if

$$(1-\gamma)(1-\delta)(1+s)\alpha > \max[1, (1+s)\beta],$$

which ensures that nonteachers cannot invade this fixation of teachers.

Remarks

Whereas the eigenvectors in Appendix 1 define the equilibria of Eq. (18.15), the corresponding eigenvalues are equal to the mean fitnesses, $\widehat{W}\,\widehat{V}$, at each of these equilibria. Our analysis shows that the globally stable equilibrium is associated with the highest mean fitness.

Fig. 18.1 (see also Fig. 18.2 lower panels) illustrates the regions in the parameter space of the two vertical transmission parameters, α and β, where each of the three equilibria given by Eqs. (18.18), (18.19), or (18.20) exist and are globally stable. Several properties of the ARUT model can be explained with reference to this (β,α)–parameter space. First, we note that evolution of teaching is more readily achieved—the teacher equilibrium given by Eq. (18.20) is more likely to be globally stable—when the increase in the efficiency of vertical transmission effected by teaching is large, ie, α is large relative to β. More specifically, we find that teaching can more easily evolve when the advantageous bar phenotype cannot be maintained in the population by social learning alone, ie, without teaching. Thus, in the left part of the figure defined by $(1+s)\beta < 1$, where the equilibrium Eq. (18.19) *does not* exist, the condition is $(1-\gamma)(1-\delta)(1+s)\alpha > 1$. By contrast, in the right part of the figure defined by $(1+s)\beta > 1$, where the equilibrium Eq. (18.19) *does* exist, the condition becomes the more stringent $(1-\gamma)(1-\delta)(1+s)\alpha > (1+s)\beta$.

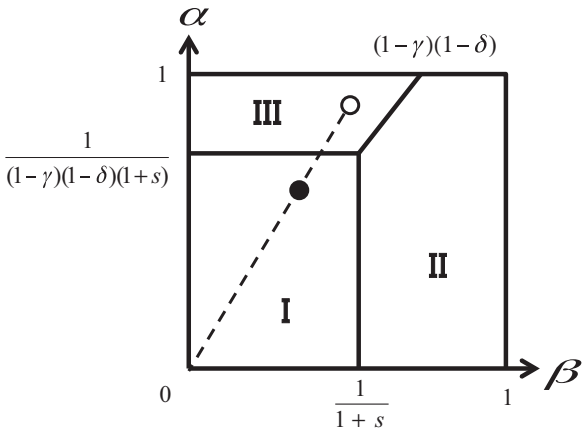

FIGURE 18.1 Depicts the mutually exclusive regions in the (β,α)–parameter space where the three edge/corner equilibria of the asexual reproduction and uniparental transmission (ARUT) model exist and are globally stable; α and β are the vertical transmission rates of the adaptive bar phenotype from teacher and nonteacher parents, respectively. Region I: corner equilibrium defined by Eq. (18.18) where nonteachers are fixed and the bar phenotype is absent. Region II: edge equilibrium defined by Eq. (18.19) where nonteachers are fixed and the bar phenotype is polymorphic. Region III: edge equilibrium defined by Eq. (18.20) where teachers are fixed and the bar phenotype is polymorphic. The open and closed circles on the broken line passing through the origin illustrate the effect of information decay due to environmental change. Information that is beneficial in the parental generation will, with a certain probability, be rendered useless in the offspring generation, with the result that the realized transmission rates of the bar phenotype (*closed circle*) are reduced from what they might be in a stable environment (*open circle*). Other parameters are: s, the viability advantage from having the bar phenotype; γ, the developmental viability cost of the neural substrate for teaching; δ, the fertility cost of the teaching act.

Second, it is not obvious whether the equilibrium frequency of the adaptive bar phenotype will be higher when teaching has evolved ($\widehat{\overline{x}}$ in Eq. (18.20)) than at the phenotypically polymorphic equilibrium without teaching ($\widehat{\overline{y}}$ in Eq. (18.19)). Nevertheless, this is always true. In fact, a necessary condition for teaching to evolve is $\frac{(1-\delta)(1+s)\alpha-1}{(1-\delta)(1+s\alpha)-1} > \frac{(1+s)\beta-1}{s\beta}$ (the frequency of the favored bar phenotype is greater when teaching is fixed than when nonteaching is fixed), which simplifies to $\frac{\alpha-\beta}{1-\beta} > \frac{\delta}{(1-\delta)s}$. This result again shows that α must be sufficiently larger than β for teaching to evolve. That is, vertical transmission of the advantageous trait by teachers must be sufficiently more reliable than from nonteachers for teaching to evolve.

Third, we consider the effect of information decay resulting from environmental change. Let α^* and β^* be the vertical transmission rates in a constant environment. Then, if ε is the rate of information decay per generation, we can write $\alpha = \alpha^*(1-\varepsilon)$ and $\beta = \beta^*(1-\varepsilon)$ for the realized transmission rates (Aoki and Feldman, 2014). Now suppose the point (β^*,α^*) lies in region III of Fig. 18.1 (open circle) where the equilibrium given by Eq. (18.20) is globally stable. Clearly, the point (β,α) lies on the straight line

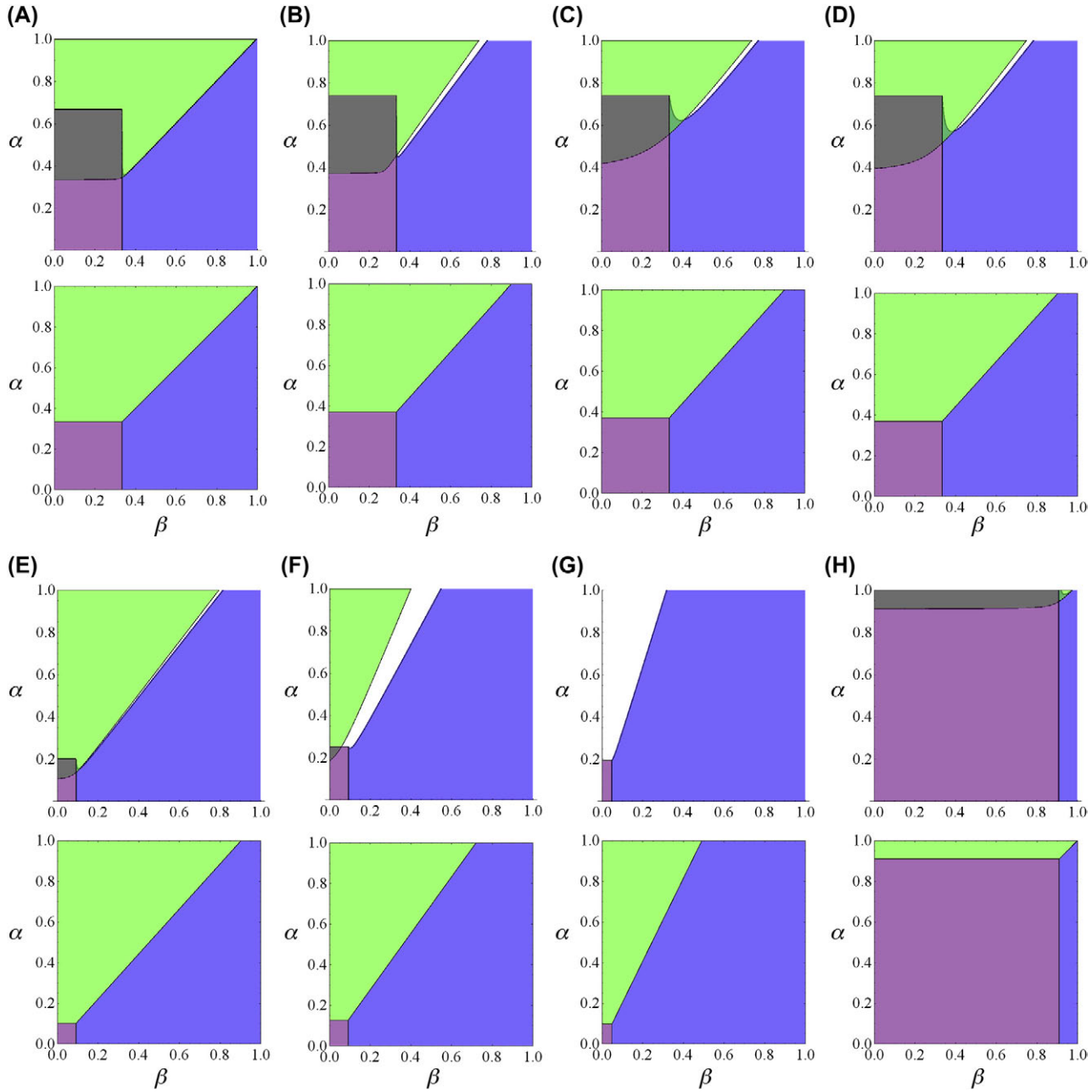

FIGURE 18.2 Comprises eight pairs of panels, Cases A to H, that differ in the values assumed for the parameters γ, δ and s. The upper panel of each pair reports the results for the SRBT model with additive vertical transmission parameters, showing the regions in the $(\beta_d,\alpha_d)-$ parameter space where the monomorphism of nonteachers without the bar phenotype—the NT_NB equilibrium, for short—exists and is locally stable (purple, left bottom); the genetic monomorphism of nonteachers with phenotypic polymorphism of the bar phenotype—the NT_B/NB equilibrium, for short—exists and is locally stable (blue, right bottom); and the genetic monomorphism of teachers with phenotypic polymorphism of the bar phenotype—the T_B/NB equilibrium, for short—exists and is locally stable (light green, left top). The lower panel uses the same colors to show the corresponding regions in the $(\beta,\alpha)-$ parameter space for the ARUT model. In the white-colored regions, which appear only in some of the upper panels, none of the three boundary equilibria is stable, implying genetic polymorphism. Some regions in the upper panels allow bistability of two (of the three) boundary equilibria. These overlapping regions are colored with a blend of the two colors: purple + light green = gray, and blue + light green = dark green.

(A) When both costs of teaching are small ($\gamma = 0.001$, $\delta = 0.001$), the results of the sexual reproduction and biparental transmission (SRBT) and ARUT models are most similar among the eight cases considered. Nevertheless, there is still a significant difference. In the SRBT model, a region of bistability (gray) can be seen in which the NT_NB equilibrium, Eq. (18.36), and the T_B/NB equilibrium, Eq. (18.43), are simultaneously stable. Here $s = 2$.

(B) When the behavioral cost of the teaching act is increased ($\gamma = 0.001$, $\delta = 0.1$), the region of existence and local stability of the T_B/NB equilibrium (light green) shrinks in both the SRBT and ARUT models as expected. This region is smaller for the former than for the latter model. In addition, a narrow region (white) appears in the SRBT model, where none of the boundary equilibria is locally stable. Here $s = 2$.

connecting the origin and (β^*,α^*). Hence, as ε increases, the point (β,α) will leave region III and enter the region where equilibrium Eq. (18.18) is stable, namely region I (closed circle). We conclude that temporal environmental variability does not favor the evolution of teaching, or, more generally speaking, an evolutionary increase in the efficiency of vertical transmission.

HAPLOID MODEL WITH SEXUAL REPRODUCTION AND BIPARENTAL TRANSMISSION (SRBT)

We now ask how the findings of section "Basic Haploid Model With Asexual Reproduction and Uniparental Transmission (ARUT)" are affected when sexual reproduction is assumed together with biparental transmission. We refer to this as the sexual reproduction and biparental transmission (SRBT) model. Among the numerous theoretical complications arising from the introduction of SRBT is that an individual may inherit the nonteaching gene a from one parent and culturally acquire the adaptive bar phenotype from the other parent. Here, we analyze a haploid model. We expect a similar result for a diploid model, because the relatedness between parent and child is the same—the fraction of genes identical by descent is one-half—in both models (Aoki and Feldman, 1997).

TABLE 18.1 Offspring Distribution From the 10 Mating Types of the Haploid Model With Sexual Reproduction and Biparental Transmission (SRBT)

Mating	$\overline{A}$	A	$\overline{a}$	a
$\overline{A}\times\overline{A}$	α_d	$1-\alpha_d$		
$\overline{A}\times A$	α_s	$1-\alpha_s$		
$\overline{A}\times\overline{a}$	$\frac{1}{2}\mu$	$\frac{1}{2}(1-\mu)$	$\frac{1}{2}\mu$	$\frac{1}{2}(1-\mu)$
$\overline{A}\times a$	$\frac{1}{2}\alpha_s$	$\frac{1}{2}(1-\alpha_s)$	$\frac{1}{2}\alpha_s$	$\frac{1}{2}(1-\alpha_s)$
$A\times A$		1		
$A\times\overline{a}$	$\frac{1}{2}\beta_s$	$\frac{1}{2}(1-\beta_s)$	$\frac{1}{2}\beta_s$	$\frac{1}{2}(1-\beta_s)$
$A\times a$		$\frac{1}{2}$		$\frac{1}{2}$
$\overline{a}\times\overline{a}$			β_d	$1-\beta_d$
$\overline{a}\times a$			β_s	$1-\beta_s$
$a\times a$				1

Phenogenotypes are: $\overline{A}$ = teacher with bar; A = teacher without bar; $\overline{a}$ = nonteacher with bar; and a = nonteacher without bar. Transmission parameters are: α_d = probability offspring acquires bar when both parents are teachers with bar; α_s = probability offspring acquires bar when one parent is a teacher with bar and the other parent does not have bar; μ = probability offspring acquires bar when one parent is a teacher with bar and the other parent is a nonteacher with bar; β_d = probability offspring acquires bar when both parents are nonteachers with bar; β_s = probability offspring acquires bar when one parent is a nonteacher with bar and the other parent does not have bar. Inequalities: $\beta_s<\alpha_s<\mu<\alpha_d<1$ and $\beta_s<\beta_d<\mu<\alpha_d<1$.

Model Description

Table 18.1 lists the 10 possible mating types among the four phenogenotypes and gives the offspring distributions from these mating types in terms of five transmission parameters. The meanings of these transmission parameters are explained in the table legend.

We assume that the fertility cost associated with the teaching act is multiplicative. Thus, the relative fertility of a mating between two bar teachers is $(1-\delta)^2$, whereas it is $1-\delta$ when only one partner is a bar teacher. Finally, we assume random mating among the four phenogenotypes. Then, the frequencies of the four phenogenotypes among the newborns after vertical transmission are

$$\begin{aligned} V\overline{x}_v &= (1-\delta)\overline{x}[(1-\delta)\overline{x}\alpha_d+(x+y)\alpha_s+\overline{y}\mu] \\ &\quad + x[(1-\delta)\overline{x}\alpha_s+\overline{y}\beta_s] \end{aligned} \tag{18.21}$$

(C) When the fixed cognitive cost of teaching is increased ($\gamma=0.1$, $\delta=0.001$), a small region (dark green) appears in the SRBT model where equilibrium NT_B/NB, given by Eq. (18.19), and equilibrium T_B/NB, given by Eq. (18.20), are both locally stable. This region of bistability also exists in the upper panels of Cases A and B, but is even smaller and hence not clearly visible. In addition, there is a region of bistability of equilibria NT_NB and T_B/NB (gray). Here $s=2$.

(D) When both costs of teaching are increased relative to Case A, but keeping their sum roughly equal to Cases B and C ($\gamma=0.05$, $\delta=0.05$), the result resembles the average of the two cases. Here $s=2$.

(E) When the selective advantage associated with the bar phenotype is greatly increased from $s=2$ in Case D to $s=10$, the regions of local stability of the nonteacher equilibria, NT_NB (purple) and NT_B/NB (blue), shrink. The qualitative results remain the same as in Case D for both the SRBT and ARUT models. Here $\gamma=0.05$, $\delta=0.05$.

(F) When both costs of teaching are increased relative to Case E ($\gamma=0.2$, $\delta=0.1$), the region where none of the boundary equilibria is locally stable (white) in the SRBT model increases in size. Accordingly, the region of bistability of equilibria NT_B/NB and T_B/NB (dark green) disappears. Here $s=10$.

(G) When all effects are large, the region where none of the boundary equilibria is locally stable (white) is large and the region of local stability of the T_B/NB equilibrium (light green) disappears in the SRBT model. This implies that coexistence of teachers and nonteachers is more likely to occur (in the SRBT model) when the benefit of the socially learned information and the two costs of teaching are large (strong selection). Here $\gamma=0.3$, $\delta=0.3$, $s=20$.

(H) When the benefit of information and the two costs of teaching are small (weak selection), the region of local stability of the T_B/NB equilibrium in the SRBT model mostly overlaps with the region of local stability of equilibrium NT_NB. A tiny region where the T_B/NB equilibrium is the unique locally stable equilibrium exists in the upper right hand corner of the upper panel where the vertical transmission efficiencies from nonteachers and teachers, β_d and αd respectively, are both high. This suggests that it is quite difficult for teachers to invade the resident nonteacher population when selection is weak. Here $\gamma=0.001$, $\delta=0.001$, $s=0.1$.

$$Vx_v = [(1-\delta)\bar{x}+x]\sqrt{V} - (1-\delta)\bar{x}[(1-\delta)\bar{x}\alpha_d + (x+y)\alpha_s + \bar{y}\mu] - x[(1-\delta)\bar{x}\alpha_s + \bar{y}\beta_s] \quad (18.22)$$

$$V\bar{y}_v = \bar{y}[(1-\delta)\bar{x}\mu + (x+y)\beta_s + \bar{y}\beta_d] + y[(1-\delta)\bar{x}\alpha_s + \bar{y}\beta_s] \quad (18.23)$$

$$Vy_v = (\bar{y}+y)\sqrt{V} - \bar{y}[(1-\delta)\bar{x}\mu + (x+y)\beta_s + \bar{y}\beta_d] - y[(1-\delta)\bar{x}\alpha_s + \bar{y}\beta_s], \quad (18.24)$$

where

$$V = (1-\delta\bar{x})^2. \quad (18.25)$$

Next, incorporating viability selection on the newborns yields

$$W\bar{x}' = (1-\gamma)(1+s)\bar{x}_v \quad (18.26)$$

$$Wx' = (1-\gamma)x_v \quad (18.27)$$

$$W\bar{y}' = (1+s)\bar{y}_v \quad (18.28)$$

$$Wy' = y_v, \quad (18.29)$$

where

$$W = (1-\gamma)(1+s)\bar{x}_v + (1-\gamma)x_v + (1+s)\bar{y}_v + y_v. \quad (18.30)$$

We have made the same assumptions on viability selection as in the ARUT model. Hence, Eqs. (18.26)–(18.30) are identical to Eqs. (18.10)–(18.14).

On substituting Eqs. (18.21)–(18.25) into Eqs. (18.26)–(18.30), we obtain the recursions over one generation:

$$WV\bar{x}' = (1-\gamma)(1+s)\{(1-\delta)\bar{x}[(1-\delta)\bar{x}\alpha_d + (x+y)\times\alpha_s + \bar{y}\mu] + x[(1-\delta)\bar{x}\alpha_s + \bar{y}\beta_s]\} \quad (18.31)$$

$$WVx' = (1-\gamma)\Big\{[(1-\delta)\bar{x}+x]\sqrt{V} - (1-\delta)\bar{x}[(1-\delta)\times\bar{x}\alpha_d + (x+y)\alpha_s + \bar{y}\mu] - x[(1-\delta)\bar{x}\alpha_s + \bar{y}\beta_s]\Big\} \quad (18.32)$$

$$WV\bar{y}' = (1+s)\{\bar{y}[(1-\delta)\bar{x}\mu + (x+y)\beta_s + \bar{y}\beta_d] + y[(1-\delta)\bar{x}\alpha_s + \bar{y}\beta_s]\} \quad (18.33)$$

$$WVy' = (\bar{y}+y)\sqrt{V} - \bar{y}[(1-\delta)\bar{x}\mu + (x+y)\beta_s + \bar{y}\beta_d] - y[(1-\delta)\bar{x}\alpha_s + \bar{y}\beta_s]. \quad (18.34)$$

Although the system (18.31)–(18.34) is much more complicated than the ARUT model, analysis of the boundary equilibria analogous to those in the ARUT model is still possible.

Identifying the Equilibria

The variable space for Eqs. (18.31)–(18.34) is a tetrahedron with four faces and six edges. The four faces are defined by $\bar{x}=0$, $x=0$, $\bar{y}=0$, or $y=0$, respectively; and the six edges by $\bar{x}+x=0$, $\bar{x}+\bar{y}=0$, $\bar{x}+y=0$, $x+\bar{y}=0$, $x+y=0$, or $\bar{y}+y=0$. Of these, all four faces and four of the six edges cannot support equilibria (except perhaps in the corners). These properties are shared by the ARUT and SRBT models. Consider, for example, the edge defined by $x+y=0$. At an equilibrium on this edge, only the two phenogenotypes, bar teacher $(\overline{A})$ and bar nonteacher $(\overline{a})$, can be present. However, from the offspring distributions in Table 18.1, we see that the three possible matings involving $\overline{A}$ and $\overline{a}$ generate the other two phenogenotypes, which says that $x+y=0$ cannot be a legitimate edge. On the edge defined by $\bar{x}+\bar{y}=0$, we can use Eqs. (18.32) and (18.34) with $\bar{x}=0$ and $\bar{y}=0$ to show that not-bar teachers (A) will be selected out because $\gamma>0$.

Thus, the only possible boundary equilibria are located on the two edges $\bar{x}+x=0$ and $\bar{y}+y=0$, which correspond to genetic monomorphisms of nonteachers and teachers, respectively. The stability properties of these genetic fixations tell us whether teaching will evolve or be lost. We investigate these equilibria in the following two subsections. The considerations of this subsection do not rule out fully polymorphic equilibria, and in fact numerical work to be described later suggests that they may exist.

Genetically Monomorphic Equilibria of Nonteachers

Set $\bar{x}=\bar{x}'=\hat{\bar{x}}=0, x=x'=\hat{x}=0, \bar{y}=\bar{y}'=\hat{\bar{y}}$, and $y=y'=\hat{y}$ in Eqs. (18.31)–(18.34). Adding Eqs. (18.33) and (18.34) gives the mean fitness at this equilibrium

$$\hat{W}\hat{V} = 1 + s\hat{\bar{y}}[2\beta_s + \hat{\bar{y}}(\beta_d - 2\beta_s)]. \quad (18.35)$$

From Eq. (18.33) it is clear that the fixation on the nonteacher-not-bar point

$$\hat{\bar{x}} = \hat{x} = \hat{\bar{y}} = 0, \hat{y} = 1 \quad (18.36)$$

always exists, and can readily be shown to be stable in the nonteacher subspace if $2(1+s)\beta_s < 1$.

Similarly, we see from Eq. (18.33) that for the equilibrium of the form $(0, 0, \hat{\bar{y}}, \hat{y})$, where allele a is fixed, but which is phenotypically polymorphic, $(0<\hat{y}<1,\ \hat{\bar{x}}=\hat{x}=0)$ to exist, $\hat{\bar{y}}$ must satisfy

$$1 + s\hat{\bar{y}}[2\beta_s + \hat{\bar{y}}(\beta_d - 2\beta_s)] = (1+s)[2\beta_s + \hat{\bar{y}}(\beta_d - 2\beta_s)].$$

That is, $\hat{\bar{y}}>0$ is the valid solution of the quadratic equation

$$f(z) \equiv s(\beta_d - 2\beta_s)z^2 + [2s\beta_s - (1+s)(\beta_d - 2\beta_s)]z + 1 - 2(1+s)\beta_s = 0. \quad (18.37)$$

Since $f(0) = 1 - 2(1+s)\beta_s$ and $f(1) = 1 - \beta_d > 0$, a unique positive equilibrium $\widehat{\overline{y}} > 0$, where $f'(\widehat{\overline{y}}) > 0$, exists if $2(1+s)\beta_s > 1$. Moreover, when it exists this positive equilibrium can also be shown to be stable to perturbations in the nonteacher subspace. Note that these considerations do not rule out other positive equilibria when $2(1+s)\beta_s < 1$.

In Appendix 2a, the stability analysis of equilibria on this edge where $\overline{a}$ and a coexist is recorded. The equilibrium with $\widehat{\overline{y}} = 0$ (only a present) is locally stable to invasion by teachers if

$$(1-\gamma)(1-\delta)(1+s)\alpha < 1, \tag{18.38}$$

which is identical in form to the corresponding result for the ARUT model. Stability properties of other equilibria on this nonteaching edge are treated numerically in the next section.

Genetically Monomorphic Equilibria of Teachers

Set $\overline{x} = \overline{x}' = \widehat{\overline{x}}, x = x' = \widehat{x}, \overline{y} = \overline{y}' = \widehat{\overline{y}} = 0$, and $y = y' = \widehat{y} = 0$ in Eqs. (18.31)–(18.34). This is the $\overline{A}$–A edge. Adding Eqs. (18.31) and (18.32) gives the mean fitness at equilibrium

$$\widehat{W}\,\widehat{V} = (1-\gamma)\{(1-\delta\widehat{\overline{x}})^2 + s(1-\delta)\widehat{\overline{x}}[(1-\delta) \times \widehat{\overline{x}}\alpha_d + 2\widehat{x}\alpha_s]\}. \tag{18.39}$$

From Eq. (18.31) it is clear that the zero equilibrium $\widehat{\overline{x}} = 0$ $(\widehat{x} = 1,\ \widehat{\overline{y}} = \widehat{y} = 0)$ always exists, and can readily be shown to be stable in the teacher subspace if $2(1-\delta)(1+s)\alpha_s < 1$.

Similarly, we see from Eq. (18.31) that a positive equilibrium with both $\overline{A}$ and A present, and which is phenotypically polymorphic, $\widehat{\overline{x}} > 0$ $(0 < \widehat{x} < 1,\ \widehat{\overline{y}} = \widehat{y} = 0)$ must satisfy

$$(1-\delta\widehat{\overline{x}})^2 + s(1-\delta)\widehat{\overline{x}}[(1-\delta)\widehat{\overline{x}}\alpha_d + 2\widehat{x}\alpha_s] = (1-\delta) \times (1+s)[(1-\delta)\widehat{\overline{x}}\alpha_d + 2\widehat{x}\alpha_s].$$

Hence, $\widehat{\overline{x}} > 0$ is the valid solution of the quadratic

$$f(z) = \{\delta^2 + s(1-\delta)[(1-\delta)\alpha_d - 2\alpha_s]\}z^2 + \{-2\delta + (1-\delta)[2(1+2s)\alpha_s - (1-\delta) \times (1+s)\alpha_d]\}z + 1 - 2(1-\delta)(1+s)\alpha_s. \tag{18.40}$$

Since $f(0) = 1 - 2(1-\delta)(1+s)\alpha_s$ and $f(1) = (1-\delta)^2 \times (1-\alpha_d) > 0$, a unique positive equilibrium $\widehat{\overline{x}} > 0$, where $f'(\widehat{\overline{x}}) > 0$, exists if $2(1-\delta)(1+s)\alpha_s > 1$. Moreover, this positive equilibrium can also be shown to be stable to perturbations in the teacher subspace when it exists. These considerations do not rule out other positive equilibria when $2(1-\delta)(1+s)\alpha_s < 1$.

From Appendix 2b, the equilibrium $\widehat{\overline{x}} = 0$ is always unstable, which was also true in the ARUT model. Stability properties of equilibria on this teaching edge are treated numerically in the next section.

Special Case of Additive Vertical Transmission Parameters

To proceed further with the analysis of the SRBT model, and to compare it with the ARUT model, we make the simplifying assumption that the vertical transmission parameters are additive. Specifically, we set

$$\alpha_d = 2\alpha_s,\ \ \beta_d = 2\beta_s,\ \ \text{and}\ \ \mu = \alpha_s + \beta_s. \tag{18.41}$$

In words, a "double dose" of either bar teachers or bar nonteachers entails twice the efficiency of each "single dose," and a "mixed dose" comprising a bar teacher and a bar nonteacher has an efficiency equal to the sum of the two respective single doses.

On substituting $\beta_d = 2\beta_s$ into Eq. (18.37), we find that there can be only one phenotypically polymorphic equilibrium,

$$\widehat{\overline{x}} = \widehat{x} = 0,\ \ \widehat{\overline{y}} = \frac{(1+s)\beta_d - 1}{s\beta_d},\ \ \widehat{y} = \frac{1-\beta_d}{s\beta_d} \tag{18.42}$$

in the nonteacher subspace (genetically monomorphic for nonteachers). Similarly, substitution of $\alpha_d = 2\alpha_s$ into Eq. (18.40) shows that there can be only one phenotypically polymorphic equilibrium,

$$\widehat{\overline{x}} = \frac{(1-\delta)(1+s)\alpha_d - 1}{(1-\delta)(1+s\alpha_d) - 1}, \widehat{x} = \frac{(1-\delta)(1-\alpha_d)}{(1-\delta)(1+s\alpha_d) - 1}, \widehat{\overline{y}} = \widehat{y} = 0 \tag{18.43}$$

in the teacher subspace (genetically monomorphic for teachers). Eqs. (18.42) and (18.43) are identical to Eqs. (18.19) and (18.20), respectively, of the ARUT model if we equate α_d to α and β_d to β.

Using numerical examples we investigate the conditions for the local stability of the three equilibria we have identified so far, ie, those given by Eqs. (18.36), (18.42), and (18.43). Fig. 18.2 comprises eight pairs of panels, where the upper panel of each pair shows the color-coded regions in the (β_d,α_d)– parameter space (α_d and β_d are the vertical transmission rates of the beneficial information when both parents are teachers and nonteachers, respectively) where these equilibria exist and are locally stable in the SRBT model. The eight panels are distinguished by differences in the values of the three other parameters: γ (the developmental cost of the neural substrate for teaching), δ (the cost of the teaching act), and s (the selective advantage gained from having the beneficial information).

In the purple, blue, and light green regions of each panel, only one of the equilibria given by Eqs. (18.36), (18.42), and (18.43), respectively, exists and is locally stable. In the gray region, equilibrium Eq. (18.36), ie, $\widehat{\overline{x}} = \widehat{x} = \widehat{\overline{y}} = 0, \widehat{y} = 1$, and equilibrium Eq. (18.43), ie, $\widehat{\overline{x}} = \frac{(1-\delta)(1+s)\alpha_d - 1}{(1-\delta)(1+s\alpha_d)-1}, \widehat{x} = \frac{(1-\delta)(1-\alpha_d)}{(1-\delta)(1+s\alpha_d)-1}, \widehat{\overline{y}} = \widehat{y} = 0,$ are both locally stable (see, eg, Panel A upper graph). Similarly, in the dark green region, equilibrium Eq. (18.42), ie, $\widehat{\overline{x}} = \widehat{x} = 0, \widehat{\overline{y}} = \frac{(1+s)\beta_d - 1}{s\beta_d}, \widehat{y} = \frac{1-\beta_d}{s\beta_d}$, and equilibrium Eq. (18.43) are both locally stable (see, eg, Panel C upper graph). Hence, the SRBT model shows bistability, ie, the evolutionary outcome depends on the initial frequencies of the four phenogenotypes. Numerical iteration of the recursion Eqs. (18.31)–(18.34) confirmed that the system converged to one of the two equilibria in these bistable cases. Moreover, in the white region none of these three boundary equilibria is locally stable, which suggests that a stable fully polymorphic equilibrium with all four phenogenotypes present exists (see, eg, Panel F upper graph). We observed convergence to such an internal equilibrium in our numerical analysis. The area of the white region appears to increase as the selection coefficients γ, δ, and s increase (compare upper graphs of Panels D, F, and G), although the dependence is not straightforward. Neither bistability nor a fully polymorphic equilibrium was observed in the ARUT model (lower graphs in Fig. 18.2).

Generally speaking, the condition for invasion by teachers is more stringent in the SRBT than in the ARUT model, where stringency is measured as the minimum value of α_d or α, respectively, that is required for invasion to succeed. Invasion by teachers cannot occur from equilibrium Eq. (18.36) in the purple and gray regions of Fig. 18.2, since this equilibrium is locally stable there. Similarly, invasion of teachers cannot occur from equilibrium Eq. (18.42) in the blue and dark green regions. These combined regions have roughly the same location and extent as the regions of global stability of the analogous equilibria Eqs. (18.18) and (18.19), respectively, of the ARUT model. However, the upper bounds of the former exceed the upper bounds of the latter, sometimes substantially. In fact, if we equate α_d of the SRBT model to α of the ARUT model, comparison of inequality Eq. (18.38) (with $\alpha_d = 2\alpha_s$) with inequality Eq. (18.16) shows that the condition for invasion by teachers from equilibrium Eq. (18.36) is exactly twice as stringent as that from the analogous equilibrium Eq. (18.18).

Another interesting difference is as follows. Recall from Subsection Remarks that in the ARUT model teaching can more easily invade (evolve) from equilibrium Eq. (18.18) than from Eq. (18.19), ie,, if the bar phenotype cannot be maintained without teaching. However, in the SRBT model the condition for invasion by teachers from equilibrium Eq. (18.42) may be less stringent than from Eq. (18.36). In all panels except perhaps Panel G, we see that the upper bound for local stability of equilibrium Eq. (18.42) is lower when $(1+s)\beta_d \approx 1$ than for equilibrium Eq. (18.36).

Finally, we note from the panels of Fig. 18.2 that environmental change disfavors the evolution of teaching.

ADDING OBLIQUE TRANSMISSION

In present-day hunter-gatherers, there is a developmental change from a reliance on vertical transmission to oblique and horizontal transmission as children mature (Hewlett et al., 2011). Vertical cultural transmission occurs from parent(s) to offspring, who also share genes identical by descent, but oblique transmission and horizontal transmission can occur between nonkin and is expected to disfavor the evolution of teaching. Here, we describe a model with oblique transmission from nonkin occurring after vertical transmission. That is, we superpose random oblique transmission on ARUT. We will refer to this model as the vertical transmission then oblique transmission (VTOT) model.

Model Description

Postreproductive teachers with the bar phenotype may have a lower relative viability, $1-\sigma$, due to the additional cost of teaching members of the next generation other than their offspring. Hence, we assume that the frequencies of the four phenogenotypes among the surviving adults who serve as exemplars for oblique transmission are

$$\overline{x}^* = \frac{(1-\sigma)\overline{x}}{1-\sigma\overline{x}}, \quad x^* = \frac{x}{1-\sigma\overline{x}}, \quad \overline{y}^* = \frac{\overline{y}}{1-\sigma\overline{x}}, \quad y^* = \frac{y}{1-\sigma\overline{x}}. \tag{18.44}$$

Since the viability selection in Eq. (18.44) acts on postreproductives, it affects only the phenotype frequencies in the next generation.

Vertical transmission first occurs according to Eqs. (18.5)–(18.9). Newborns who fail to obtain the beneficial information from their parents have a second chance, when they encounter *and* acquire the bar phenotype from surviving adult teachers and nonteachers with the bar phenotype at rates θ and ρ, respectively ($0 \le \rho < \theta < 1$). We make the same assumptions regarding viability selection during maturation as in the ARUT and SRBT models. Hence, the frequencies of the four phenogenotypes among the reproductive adults of the next generation are

$$W\overline{x}' = (1-\gamma)(1+s)[\overline{x}_v + x_v(\theta\overline{x}^* + \rho\overline{y}^*)], \tag{18.45}$$

$$Wx' = (1-\gamma)x_v[1-(\theta\overline{x}^* + \rho\overline{y}^*)], \tag{18.46}$$

$$W\bar{y}' = (1+s)\left[\bar{y}_v + y_v(\theta\bar{x}^* + \rho\bar{y}^*)\right], \tag{18.47}$$

$$Wy' = y_v[1 - (\theta\bar{x}^* + \rho\bar{y}^*)], \tag{18.48}$$

where

$$\begin{aligned} W =& (1-\gamma)(1+s)[\bar{x}_v + x_v(\theta\bar{x}^* + \rho\bar{y}^*)] + (1-\gamma) \\ & \times x_v[1 - (\theta\bar{x}^* + \rho\bar{y}^*)] + (1+s)\left[\bar{y}_v + y_v(\theta\bar{x}^* + \rho\bar{y}^*)\right] \\ & + y_v[1 - (\theta\bar{x}^* + \rho\bar{y}^*)]. \end{aligned} \tag{18.49}$$

For example, of the two terms in square brackets in Eq. (18.45), the first and second give the frequencies of previability-selection individuals with the teacher genotype that acquired the bar phenotype by vertical and oblique transmission, respectively. The recursions over one generation for the VTOT model are obtained by substituting $\bar{x}_v$, x_v, $\bar{y}_v$, and y_v from Eqs. (18.5)–(18.9), and $\bar{x}^*$, x^*, $\bar{y}^*$, and y^* from Eq. (18.45) into Eq. (18.49).

Conditions for Invasion by Teachers

A full analysis of the VTOT model, even numerically, has proved difficult because of the large number of parameters. We restrict ourselves to obtaining the genetically monomorphic equilibria of nonteachers and the conditions for the invasion of teachers from these equilibria. The invasion conditions for the VTOT model can then be compared to those for the ARUT model in which there is no oblique transmission.

At a genetically monomorphic equilibrium of nonteachers

$$\hat{W}\hat{V} = 1 + s\hat{\bar{y}}\left(\beta + \rho - \beta\rho\hat{\bar{y}}\right), \tag{18.50}$$

since $\hat{\bar{x}} = \hat{x} = \hat{\bar{x}}_v = x_v = \bar{x}^* = x^* = 0$. The zero equilibrium $\hat{\bar{y}} = 0$ always exists, and can be shown to be stable in the nonteacher subspace if $(1+s)(\beta+\rho) < 1$.

A positive equilibrium $\hat{\bar{y}} > 0$ must satisfy

$$1 + s\hat{\bar{y}}\left(\beta + \rho - \beta\rho\hat{\bar{y}}\right) = (1+s)\left(\beta + \rho - \beta\rho\hat{\bar{y}}\right)$$

Rearranging, we see that $\hat{\bar{y}} > 0$ is the valid solution of

$$\begin{aligned} f(z) \equiv s\beta\rho z^2 - [s(\beta+\rho) + (1+s)\beta\rho]z + (1+s)(\beta+\rho) \\ - 1 = 0, \end{aligned} \tag{18.51}$$

which is a quadratic equation that is convex downward when $\rho > 0$. Since $f(0) = (1+s)(\beta+\rho) - 1$ and $f(1) = -(1-\beta)(1-\rho) < 0$, there is a unique positive equilibrium if and only if $(1+s)(\beta+\rho) > 1$. On the other hand, we obtain

$$\hat{\bar{y}} = \frac{(1+s)\beta - 1}{s\beta} \tag{18.52}$$

if $\rho = 0$, which is valid for $(1+s)\beta > 1$ and identical to Eq. (18.19) of the ARUT model.

Linearization of the recursions for the VTOT model around either the zero or the positive equilibrium yields a reducible 3×3 coefficient matrix. It can be shown that the positive equilibrium is locally stable in the nonteacher subspace when it exists. Local stability to invasion of teachers is governed by a 2×2 positive submatrix, which yields a very complicated quadratic characteristic polynomial.

Henceforth in this section, we consider only the special case of $\rho\hat{\bar{y}} = 0$. That is, we consider the local stability to invasion by teachers of the zero equilibrium, $\hat{\bar{y}} = 0$, and of the phenotypically polymorphic equilibrium that is given by Eq. (18.52) when $\rho = 0$. Recall that ρ and θ are the oblique transmission rates—the products of encounter and acquisition rates—from nonteachers and teachers, respectively. Anthropological research on hunter-gatherers suggests that adolescents choose exemplars for oblique transmission based on the prosocial characteristics of adults (Hewlett, 2013). If teachers are preferred as exemplars for oblique transmission, then it is reasonable as a first approximation to set $\rho = 0$ and $\theta > 0$.

When $\rho\hat{\bar{y}} = 0$, we can show that the zero equilibrium, $\hat{\bar{y}} = 0$, is invadable by teachers if

$$(1-\gamma)(1-\delta)(1+s)\alpha > 1, \tag{18.53}$$

and the phenotypically polymorphic equilibrium, Eq. (18.52), is invadable if

$$(1-\gamma)(1-\delta)(1+s)\alpha > (1+s)\beta. \tag{18.54}$$

Clearly, these invasion conditions are identical to those for the ARUT model, which are given by Eqs. (18.16) and (18.17), respectively. However, these conditions do not ensure fixation of teachers, as would be true of the ARUT model. In fact, Fig. 18.3A illustrates a case suggesting the existence of a stable fully polymorphic equilibrium when Eq. (18.54) is satisfied.

ADDING HORIZONTAL TRANSMISSION (VTHT)

In this section, we describe a model with horizontal transmission from nonkin occurring after vertical transmission, which we call the vertical transmission then horizontal transmission (VTHT) model. Then, we present a limited analysis to obtain the genetically monomorphic equilibria of nonteachers and the conditions for the invasion of teachers from these equilibria.

Model Description

Vertical transmission first occurs according to Eqs. (18.5)–(18.9). Newborns who fail to obtain the beneficial information from their parents have a second chance,

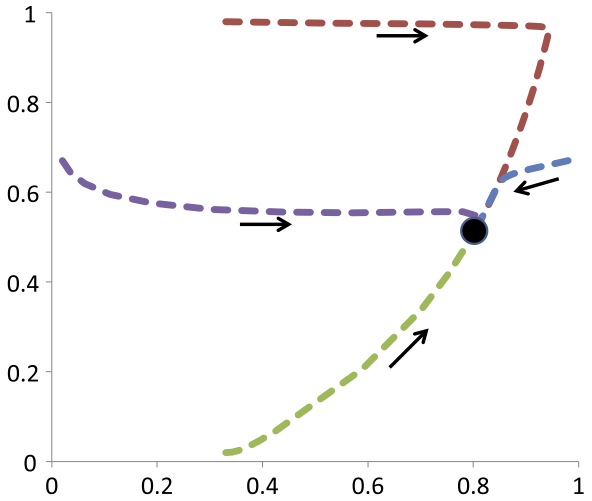

FIGURE 18.3A Numerically obtained coevolutionary trajectories for the VTOT model are shown by broken lines. The trajectories have been projected on to the two-dimensional variable space where the horizontal axis corresponds to the frequency of the bar phenotype $(\bar{x}+\bar{y})$ and the vertical axis corresponds to the frequency of teachers $(\bar{x}+x)$. Convergence to the fully polymorphic equilibrium, $\hat{\bar{x}} = 0.4786$, $\hat{x} = 0.0408$, $\hat{\bar{y}} = 0.3268$, $\hat{y} = 0.1538$, indicated by the filled circle is suggested. Parameter values are $\alpha = 0.9$, $\beta = 0.6$, $\gamma = 0.1$, $\delta = 0.1$, $s = 1$, $\sigma = 0.1$, $\theta = 0.4$, and $\rho = 0$.

when they encounter and acquire the bar phenotype from other newborns that have succeeded in doing so. The horizontal transmission rates from bar teachers and bar nonteachers of the same generation are θ and ρ, respectively $(0 \le \rho < \theta < 1)$; we use the same symbols as for the VTOT model, since they play analogous roles in the two models. In addition, we assume that bar teachers incur a cost due to the teaching act, proportional to the frequency of nonbar individuals of the same generation $(x_v + y_v)$, where the proportionality constant is η. Then

$$W\bar{x}' = (1-\gamma)(1+s)\{\bar{x}_v[1-\eta(x_v+y_v)] + x_v(\theta\bar{x}_v + \rho\bar{y}_v)\} \tag{18.55}$$

$$Wx' = (1-\gamma)x_v[1-(\theta\bar{x}_v + \rho\bar{y}_v)] \tag{18.56}$$

$$W\bar{y}' = (1+s)[\bar{y}_v + y_v(\theta\bar{x}_v + \rho\bar{y}_v)] \tag{18.57}$$

$$Wy' = y_v[1-(\theta\bar{x}_v + \rho\bar{y}_v)], \tag{18.58}$$

where

$$\begin{aligned} W = {} & (1-\gamma)(1+s)\{\bar{x}_v[1-\eta(x_v+y_v)] + x_v(\theta\bar{x}_v + \rho\bar{y}_v)\} \\ & + (1-\gamma)x_v[1-(\theta\bar{x}_v + \rho\bar{y}_v)] + (1+s)[\bar{y}_v + y_v \\ & \times (\theta\bar{x}_v + \rho\bar{y}_v)] + y_v[1-(\theta\bar{x}_v + \rho\bar{y}_v)]. \end{aligned} \tag{18.59}$$

The recursions over one generation for this VTHT model are obtained by substituting $\bar{x}_v$, x_v, $\bar{y}_v$, and y_v from Eqs. (18.5)–(18.9) into Eqs. (18.55)–18.59).

Conditions for Invasion by Teachers

At a genetically monomorphic equilibrium of nonteachers

$$\hat{W}\hat{V} = 1 + s\beta\hat{\bar{y}}(1+\rho-\beta\rho\hat{\bar{y}}). \tag{18.60}$$

The zero equilibrium, $\hat{\bar{y}} = 0$, always exists and is stable in the nonteacher subspace if $(1+s)\beta(1+\rho) < 1$.

Eqs. (18.57) and (18.60) entail that a positive equilibrium, $\hat{\bar{y}} > 0$, must satisfy

$$1 + s\beta\hat{\bar{y}}(1+\rho-\beta\rho\hat{\bar{y}}) = (1+s)\beta(1+\rho-\beta\rho\hat{\bar{y}})$$

where we have used $\hat{\bar{y}}_v = \beta\hat{\bar{y}}$. Hence, $\hat{\bar{y}} > 0$ is the valid solution of

$$\begin{aligned} f(z) \equiv {} & s\beta^2\rho z^2 - [s(1+\rho) + (1+s)\beta\rho]\beta z + (1+s) \\ & \times \beta(1+\rho) - 1 = 0. \end{aligned} \tag{18.61}$$

When $\rho > 0$, Eq. (18.61) is a quadratic that is convex downward. Moreover, since $f(0) = (1+s)\beta(1+\rho) - 1$ and $f(1) = -(1-\beta)(1-\beta\rho) < 0$, there is a unique positive equilibrium if and only if $(1+s)\beta(1+\rho) > 1$. On the other hand, we obtain

$$\hat{\bar{y}} = \frac{(1+s)\beta - 1}{s\beta} \tag{18.62}$$

if $\rho = 0$, which is valid for $(1+s)\beta > 1$ and identical to Eq. (18.19) of the ARUT model.

Linearization of the recursions for the VTHT model around either the zero or the positive equilibrium yields a reducible 3×3 coefficient matrix. It can be shown that the positive equilibrium is locally stable in the nonteacher subspace when it exists. Local stability to invasion of teachers is governed by a very complicated quadratic characteristic polynomial.

Subsequently, we restrict our attention to the special case of $\rho\hat{\bar{y}}_v = \rho\hat{\bar{y}} = 0$. That is, we consider the local stability to invasion by teachers of the zero equilibrium, $\hat{\bar{y}} = 0$, and of the phenotypically polymorphic equilibrium that is given by Eq. (18.62) when $\rho = 0$. As in the VTOT model, our justification for the latter is that teachers may be preferred as exemplars for horizontal transmission (Hewlett, 2013), so it is reasonable to set $\rho = 0$ and $\theta > 0$.

When $\rho\hat{\bar{y}} = 0$, the zero equilibrium, $\hat{\bar{y}} = 0$, is invadable by teachers if

$$(1-\gamma)(1-\delta)(1+s)\alpha(1-\eta) > 1, \tag{18.63}$$

and the phenotypically polymorphic equilibrium, Eq. (18.62), is invadable if

$$(1-\gamma)(1-\delta)(1+s)\alpha\left[1-\frac{\eta(1+s)(1-\beta)}{s}\right] > (1+s)\beta. \tag{18.64}$$

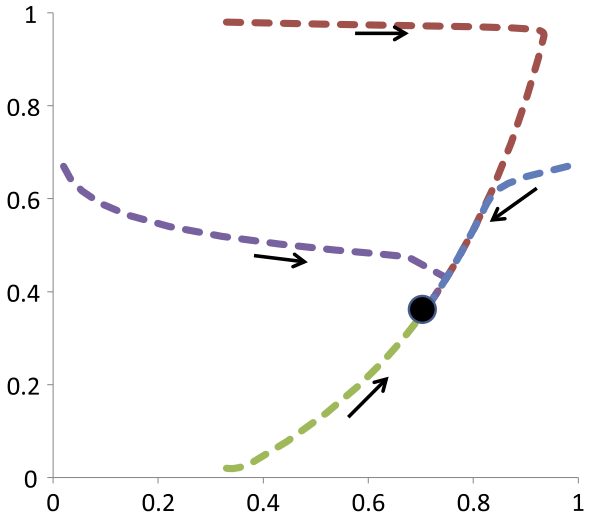

FIGURE 18.3B Numerically obtained coevolutionary trajectories for the VTHT model are shown by broken lines. The trajectories have been projected on to the two-dimensional variable space where the horizontal axis corresponds to the frequency of the bar phenotype $(\bar{x}+\bar{y})$ and the vertical axis corresponds to the frequency of teachers $(\bar{x}+x)$. Convergence to the fully polymorphic equilibrium, $\hat{\bar{x}} = 0.3100$, $\hat{x} = 0.0365$, $\hat{\bar{y}} = 0.3891$, $\hat{y} = 0.2644$, indicated by the filled circle, is suggested. Parameter values are $\alpha = 0.9$, $\beta = 0.6$, $\gamma = 0.1$, $\delta = 0.1$, $s = 1$, $\eta = 0.1$, $\theta = 0.4$, and $\rho = 0$.

Clearly, both invasion conditions are more stringent than the corresponding conditions for the VTOT—also the ARUT—model. We consider the reasons for the differing predictions derived from the VTOT and VTHT models in the Discussion section. Moreover, these conditions do not ensure fixation of teachers. In fact, Fig. 18.3B illustrates a case suggesting the existence of a stable fully polymorphic equilibrium when Eq. (18.64) is satisfied.

DISCUSSION

We investigated the theoretical conditions for the evolution of parental teaching of an advantageous cultural trait. The ARUT model posits asexual reproduction and uniparental transmission. It can be analyzed completely and shows how the efficiencies of vertical transmission of beneficial information, costs to the parent, and benefit to the offspring interact to determine whether teaching can evolve (see Fig. 18.1). The negative effect of environmental change, namely making fixation of teaching unstable and fixation of nonteaching stable, was also revealed. Many predictions of the ARUT model carry over qualitatively to the SRBT model, the VTOT model, and the VTHT model. An important difference is that a genetic polymorphism of teachers and nonteachers may arise in the latter three models, but is not possible in the ARUT model.

A major shortcoming of the ARUT model is that it assumes asexual reproduction, which facilitates analysis but entails that the genetic relatedness between parent and child is 100%. Hence, a quantitatively valid inclusive fitness argument applicable to animals and humans cannot be made based on this model. This deficiency is remedied by the SRBT model, which assumes sexual reproduction and biparental transmission. Here, the relatedness between parent and child is one-half. (We note that considerations of relatedness alone would suggest that more teaching should occur among asexually reproducing organisms.)

In the putative cases of teaching in felids it is the mother that teaches its cubs how to catch prey, whereas in raptors both parents participate in teaching their fledglings to hunt (Caro and Hauser, 1992). In human hunter-gatherers, cultural traits are often transmitted in a sex-limited way from mother to daughter or from father to son, but there may also be some influence of the opposite-sex parent (Hewlett and Cavalli-Sforza, 1986; Hewlett et al., 2011; Hewlett, 2013). The SRBT model applies to raptors and to human hunter-gatherers if we assume that, in terms of fitness, both parents suffer the same costs and that offspring of both sexes receive the same benefit.

The predictions of the SRBT model are often consistent with those of the ARUT model. Thus, the panels of Fig. 18.2 show that parental teaching is more likely to evolve when the costs to the parents are small and the benefit to the offspring is large. Similarly, parental teaching is favored when it significantly improves the efficiency of vertical transmission, and when the environment is stable. There are however some notable differences, and where a discrepancy exists, the predictions of the SRBT model are likely to be more pertinent in nature.

One major difference is that the condition for teaching to invade from the nonteacher fixation equilibrium with the adaptive phenotype absent—equilibrium Eq. (18.36) of the SRBT model and equilibrium Eq. (18.18) of the ARUT model—is twice as stringent for the former then for the latter model. This is because of the twofold difference in the relatedness between parent and child in the two models. As a result, the SRBT model predicts that invasion by teachers is relatively more likely when the adaptive phenotype can be maintained in the population without teaching—ie, from equilibrium Eq. (18.42)—when $(1 + s)\beta$ is slightly greater than 1.

Another major difference between the ARUT and SRBT models is that fully polymorphic equilibria, with all four phenogenotypes present, may exist in the SRBT model. These equilibria can be unstable which entails bistability, or globally stable as suggested by numerical work. In the former case, whether or not teaching evolves depends on the initial frequencies of the phenogenotypes. In the latter case, the population evolves to a state in which teachers and nonteachers coexist. That cultural diversity (and genetic diversity at the teacher/nonteacher locus) can be maintained under biparental transmission in the SBRT, VTOT, and VTHT models suggests that having even more

exemplars available to a juvenile may make the maintenance of genetic diversity even more likely (Fogarty et al., 2015).

These considerations are reminiscent of the discussion around the cost of sex in evolutionary genetics (eg, Maynard Smith, 1978). Consider a haploid population with alleles *A*/*a* at one locus and *D*/*d* at a second locus, with fitnesses w_1, w_2, w_3, and w_4 for the haplotypes *AD*, *Ad*, *aD*, and *ad*, respectively. In the absence of recombination, the haplotype with the largest w_i will be fixed. Now suppose $w_1, w_4 > w_2, w_3$. Then, a bistable situation can arise in the presence of recombination if $1 - r < w_1/w_4 < (1 - r)^{-1}$, where r is the recombination rate. That is, when this inequality is satisfied, fixations on *AD* and *ad* are both locally stable. This interaction of recombination with genetic epistasis is analogous to the effect of the interaction between the teaching locus and the bar/not-bar phenotype in the SRBT model. A major qualitative difference, however, is that the SRBT model seems to allow full polymorphism to be stable for some parameter values, while this is not seen in the two-locus haploid genetic model with sexual reproduction (Feldman, 1971).

In Table 18.1, if we set $\alpha_d = \beta_d = 1$, $\alpha_s = \beta_s = 1/2$, and $\mu = 1$, the transmission system becomes identical to that of the two-locus system with free recombination ($r = 1/2$). In this case the analogs to fixation on *AD* and *aD* are the fixation points $\widehat{x} = 1$ and $\widehat{y} = 1$, respectively. With γ, δ, and s all positive, both of these are locally stable, and their domains of attraction are most likely separated by a surface in the frequency simplex. In this extreme case, however, it is unlikely that any complete polymorphism can be stable, which we have seen may occur in the more general SRBT model.

Let us now briefly review the VTOT and VTHT models, which add oblique and horizontal transmission, respectively, between nonkin to the ARUT model. The cost of the teaching act can be readily incorporated for intragenerational interactions, in particular horizontal transmission (Fogarty et al., 2011). Thus, this cost is proportional to the frequency of not-bar individuals—represented in Eq. (18.55) as $\eta(x_v + y_v)$—and is incurred "only in the presence of a naïve observer" (Caro and Hauser, 1992). Similarly, if there are no fertility differences other than those due to teaching, the cost of the teaching act for vertical transmission can reasonably be incorporated as a *fixed* reduction of fertility, δ (Creanza et al., 2013). On the other hand, there is apparently no natural way to incorporate the cost of the teaching act for oblique transmission, and Eq. (18.44) must be regarded in that light.

We have restricted our analyses of the VTOT and VTHT models to obtaining the conditions for invasion by teachers. Moreover, for invasion from the phenotypically polymorphic equilibrium Eq. (18.52) or Eq. (18.62), we assume that bar nonteachers are not sought as exemplars for oblique or horizontal transmission, ie, we set $\rho = 0$ in both models. Under these simplifying assumptions, we find that the invasion conditions for the VTOT model are the same as for the ARUT model. On the other hand, they are more stringent for the VTHT model. That is, horizontal but not oblique transmission between nonkin, superposed on vertical transmission, makes it more difficult for teaching to invade. This difference between the predicted effects of oblique and horizontal transmission may be ascribed to our assumption in Eq. (18.44) that the cost of the teaching act for oblique transmission is incurred by postreproductives. In addition, numerical work suggests that stable fully polymorphic equilibria are possible in both the VTOT (Fig. 18.3A) and VTHT (Fig. 18.3B) models.

The agent-based simulation model of Premo (2015) incorporated a geographically distributed array of groups. The cultural transmission to an individual from a given group depended on the distance of the transmitting individuals' groups from the residence group of the learner. This model (see also Premo and Scholnick, 2011) did not include fitness differences between individuals with and without the cultural variant. Nor did teaching individuals have any character that distinguished them from randomly chosen new teachers. Thus the focus was on the role of population size and geographic radius in which learning (and hence, teaching) could occur, both of which affected ultimate cultural diversity.

An entirely different model was analyzed by Nakahashi (2015) who assumed that teaching behavior itself was culturally transmitted. The focus of this study was the effect of teaching on the number of traits acquired by social and individual learning, respectively. The model was developed in a context of an infinite number of possible cultural traits, some of which gave their carriers a selective advantage. An ESS (evolutionarily stable strategy) argument was used to ascertain conditions on the numbers of individually and socially acquired traits, the accuracy of cultural transmission, and amount by which teaching increased the amount of transmission that would promote the increase of teaching in a large population. Unlike our model, transmission of the teaching trait and the trait being taught were both cultural and at the same rate. Since teaching was a socially transmitted trait in this model, its increase depended strongly on social learning.

To the best of our knowledge, Fogarty et al. (2011) was the first paper to explicitly investigate the conditions for the evolution of teaching *sensu* Caro and Hauser (1992). In addition to demonstrating the importance of inclusive fitness effects, they show that teaching is more likely to invade when the sum of the efficiencies (probabilities) of acquisition of the beneficial information by individual learning and by social learning without teaching is neither too low nor too high. We have ignored individual learning in our paper, but the additive case of the SRBT model (see Subsection

Special Case of Additive Vertical Transmission Parameters) yields a result that is concordant with Fogarty et al. (2011). Namely, it predicts that teaching is more likely to invade when vertical transmission of beneficial information from nonteachers is of intermediate efficiency. Specifically, the optimal transmission rate when both nonteacher parents possess the beneficial information is slightly greater than $1/(1+s)$, where s is the selective advantage associated with the beneficial information (see Fig. 18.2). Interestingly, this entails that the adaptive phenotype can be maintained in the population without teaching.

Fogarty et al. (2011), among others, point out that cumulative culture, a characteristic of modern humans, is likely made possible by the high-fidelity social transmission of information achieved by teaching. Let us consider two contrasting aspects of this claim. First, a learning schedule is defined to be a broad developmental pattern over a single individual's lifetime in the differential use of individual learning and social learning. Borenstein et al. (2008) and Aoki (2010) define "social-learner-explorer" to be a learning schedule in which a phenotype acquired by social learning is subsequently modified by individual learning. Such a learning schedule is believed to underlie cumulative culture (Tomasello, 1999). Aoki et al. (2012) argued that social-learner-explorer can be evolutionarily stable in a constant—and by extension a relatively stable—environment, only if the efficiency of social learning among naïve newborns is high (relative to the efficiency of individual learning). Hence, the evolution of teaching might indeed facilitate the evolution of social-learner-explorer and as a result pave the way for cumulative culture.

Second, the fidelity of social learning and the innovation rate are both strongly and positively correlated with the amount of cultural variation that can be maintained in a population (Strimling et al., 2009; Lehmann et al., 2011; Aoki et al., 2011). We have shown in this chapter that temporal environmental stability favors the evolution of parental teaching or, more generally, an evolutionary increase in the efficiency of vertical transmission. However, environmental stability also has the effect of selecting for a decreased reliance on individual learning (eg, Feldman et al., 1996; Wakano and Aoki, 2006), which entails that innovativeness may be reduced. Hence, we suggest that high-fidelity social learning and high innovative ability may simultaneously evolve only within a limited range of environmental stability, with the consequence that a learning strategy supportive of complex culture will be an evolutionary rarity.

As for cumulative culture, some previous theoretical studies have found that the amount of cultural accumulation will be limited when the cost of learning is modeled in terms of decreased reproduction time during an individual's life history (Lehmann et al., 2013; Wakano and Miura, 2014; Kobayashi et al., 2015). In this chapter, we studied the cost of teaching, instead of learning, and found that the dynamics become complicated because learners do not always carry the teaching allele. It would be interesting to see whether cultural accumulation could be an evolutionary outcome for models in which the cost of teaching is explicitly a function of life history.

We note that continuous phenotypic variation, as modeled by Eq. (18.1) for example, is more realistic than dichotomous variation; genetic polymorphism would translate into a continuous spectrum for the predilection and aptitude for teaching. While there is an increasing number of genome-wide association studies (GWAS) of children's achievement in schools (eg, Domingue et al., 2014; Rietveld et al., 2015), none of these studies have directly addressed variation in teaching as a relevant covariate, although other covariates related to school environments are sometimes discussed (Domingue et al., 2015). One might ask whether these GWAS studies implicitly extend the relevance of Murray Gell-Mann's quote, at the beginning of this chapter, to elementary and high schools as well.

APPENDICES

Appendix 1. Analysis of Asexual Reproduction and Uniparental Transmission (ARUT) Dynamics in Eq. (18.15)

The eigenvalues and corresponding eigenvectors of the coefficient matrix in Eq. (18.15) are

$$\lambda_1 = (1-\gamma)(1-\delta)(1+s)\alpha \tag{A1a}$$

$$v_1^T = \left(\frac{(1-\delta)(1+s)\alpha - 1}{(1-\delta)(1+s\alpha)-1}, \frac{(1-\delta)(1-\alpha)}{(1-\delta)(1+s\alpha)-1}, 0, 0\right) \tag{A1b}$$

$$\lambda_2 = 1-\gamma \tag{A1c}$$

$$v_2^T = (0,1,0,0) \tag{A1d}$$

$$\lambda_3 = (1+s)\beta \tag{A1e}$$

$$v_3^T = \left(0, 0, \frac{(1+s)\beta - 1}{s\beta}, \frac{1-\beta}{s\beta}\right) \tag{A1f}$$

$$\lambda_4 = 1 \tag{A1g}$$

$$v_4^T = (0,0,0,1). \tag{A1h}$$

Using the argument of Wakano et al. (2004), each nonnegative eigenvector, normalized so that the elements sum to unity, defines an equilibrium, and there is global convergence to the eigenvector corresponding to the maximal eigenvalue.

Equilibrium given by vector v_4^T always exists and is globally stable if $(1+s)\beta < 1$ ($\lambda_3 < \lambda_4$) and $(1-\gamma)(1+s)\alpha < 1$ ($\lambda_1 < \lambda_4$). Equilibrium given by vector v_3^T exists if and only if $(1+s)\beta > 1$. It is stable to perturbations in the nonteacher subspace when it exists ($\lambda_3 > \lambda_4$). When it exists it is stable if $(1-\gamma)(1-\delta)(1+s)\alpha < (1+s)\beta$ (ie, $\lambda_1 < \lambda_3$).

Equilibrium given by vector v_1^T exists if and only if $(1-\delta)(1+s)\alpha > 1$. When it exists it is stable to perturbations in the teacher subspace ($\lambda_1 > \lambda_2$) and it is globally stable if $(1-\gamma)(1-\delta)(1+s)\alpha > max[1,\ (1+s)\beta]$ (ie, $\lambda_1 > \lambda_3, \lambda_4$).

condition. Specifically, for the SRBT model the zero equilibrium $\widehat{\bar{y}} = 0$ is locally stable to invasion by teachers if

$$(1-\gamma)(1-\delta)(1+s)\alpha_s < 1. \tag{A2b}$$

b. For local stability of equilibria on the teaching edge $(\widehat{\bar{x}}, \widehat{x}, 0, 0)$, we linearize Eqs. (18.31)–(18.34) around either the zero or the/a positive equilibrium, which yields a reducible 3×3 coefficient matrix. Local stability to invasion by nonteachers is governed by a 2×2 positive submatrix, which yields the characteristic (quadratic) polynomial

$$\varphi(\lambda) = \begin{vmatrix} \dfrac{(1+s)\left[(1-\delta)\mu\widehat{\bar{x}} + \beta_s\widehat{x}\right]}{\widehat{W}\widehat{V}} - \lambda & \dfrac{(1+s)(1-\delta)\alpha_s\widehat{\bar{x}}}{\widehat{W}\widehat{V}} \\ \dfrac{1-\delta\widehat{\bar{x}} - \left[(1-\delta)\mu\widehat{\bar{x}} + \beta_s\widehat{x}\right]}{\widehat{W}\widehat{V}} & \dfrac{1-\delta\widehat{\bar{x}} - (1-\delta)\alpha_s\widehat{\bar{x}}}{\widehat{W}\widehat{V}} - \lambda \end{vmatrix}, \tag{A2c}$$

where $\widehat{W}\widehat{V}$ is the mean fitness given by Eq. (18.39).

In particular, substitution of $\widehat{\bar{x}} = 0$ into Eq. (A2c) shows that the zero equilibrium $\widehat{\bar{x}} = 0$ is always unstable, which was also true of the ARUT model.

Appendix 2. Stability in the Sexual Reproduction and Biparental Transmission (SRBT) Model

a. For local stability of equilibria on the nonteaching edge $(0, 0, \widehat{\bar{y}}, \widehat{y})$, we linearize Eqs. (18.31)–(18.34) around either the zero or the/a positive equilibrium, which yields a reducible 3×3 coefficient matrix. Local stability to invasion by teachers is governed by a 2×2 positive submatrix, which yields the characteristic polynomial (quadratic)

$$\phi(\lambda) = \begin{vmatrix} \dfrac{(1-\gamma)(1-\delta)(1+s)\left(\mu\widehat{\bar{y}} + \alpha_s\widehat{y}\right)}{\widehat{W}\widehat{V}} - \lambda & \dfrac{(1-\gamma)(1+s)\beta_s\widehat{\bar{y}}}{\widehat{W}\widehat{V}} \\ \dfrac{(1-\gamma)(1-\delta)\left(1-\mu\widehat{\bar{y}} - \alpha_s\widehat{y}\right)}{\widehat{W}\widehat{V}} & \dfrac{(1-\gamma)\left(1-\beta_s\widehat{\bar{y}}\right)}{\widehat{W}\widehat{V}} - \lambda \end{vmatrix}, \tag{A2a}$$

where $\widehat{W}\widehat{V}$ is the mean fitness given by Eq. (18.35).

In particular, for the zero equilibrium Eq. (18.36), we find on substituting $\widehat{\bar{y}} = 0$ into Eq. (18.38) that the maximal eigenvalue is $(1-\gamma)(1-\delta)(1+s)\alpha_s$, which is identical in form to Eq. (18.16) (ie, λ_1 in the ARUT model). However, for the SRBT model it is a local condition, whereas in the ARUT model it provides a global

ACKNOWLEDGMENTS

This research was supported in part by Monbukagakusho grant 22101004 to Kenichi Aoki and Joe Yuichiro Wakano and by NIH grant GM28016 to Marcus W. Feldman. We thank Yutaka Kobayashi for comments.

The authors would like to acknowledge the John Templeton Foundation.

REFERENCES

Aoki, K., 2010. Evolution of the social-learner-explorer strategy in an environmentally heterogeneous two-island model. Evolution 64, 2575–2586.

Aoki, K., Feldman, M.W., 1987. Toward a theory for the evolution of cultural communication: coevolution of signal transmission and reception. Proceedings of the National Academy of Sciences of the United States of America 84, 7164–7168.

Aoki, K., Feldman, M.W., 1997. A gene-culture coevolutionary model for brother-sister mating. Proceedings of the National Academy of Sciences of the United States of America 94, 13046–13050.

Aoki, K., Feldman, M.W., 2014. Evolution of learning strategies in temporally and spatially variable environments: a review of theory. Theoretical Population Biology 91, 3–19.

Aoki, K., Lehmann, L., Feldman, M.W., 2011. Rates of cultural change and patterns of cultural accumulation in stochastic models of social transmission. Theoretical Population Biology 79, 192–202.

Aoki, K., Wakano, J.Y., Feldman, M.W., 2005. The emergence of social learning in a temporally changing environment: a theoretical model. Current Anthropology 46, 334–340.

Aoki, K., Wakano, J.Y., Lehmann, L., 2012. Evolutionarily stable learning schedules and cumulative culture in discrete generation models. Theoretical Population Biology 81, 300–309.

Borenstein, E., Feldman, M.W., Aoki, K., 2008. Evolution of learning in fluctuating environments: when selection favors both social and exploratory individual learning. Evolution 62, 586–602.

Boyd, R., Richerson, P.J., 1985. Culture and the Evolutionary Process. Univ. Chicago Press, Chicago.

Byrne, R.W., Rapaport, L.G., 2011. What are we learning from teaching? Animal Behaviour 82, 1207–1211.

Caro, T.M., Hauser, M.D., 1992. Is there teaching in nonhuman animals? The Quarterly Review of Biology 67, 151–174.

Cavalli-Sforza, L.L., Feldman, M.W., 1973. Models for cultural inheritance. I. Group mean and within group variation. Theoretical Population Biology 4, 42–55.

Cavalli-Sforza, L.L., Feldman, M.W., 1978. Darwinian selection and "altruism". Theoretical Population Biology 14, 268–280.

Cavalli-Sforza, L.L., Feldman, M.W., 1981. Cultural Transmission and Evolution: A Quantitative Approach. Princeton University Press, Princeton, N.J.

Creanza, N., Fogarty, L., Feldman, M.W., 2013. Exploring cultural niche construction from the Paleolithic to modern hunter-gatherers. In: Akazawa, T., Nishiaki, Y., Aoki, K. (Eds.), Dynamics of Learning in Neanderthals and Modern Humans, Cultural Perspectives, vol. 1. Springer, Tokyo, pp. 211–228.

Domingue, B.W., Fletcher, J., Conley, D., Boardman, J.D., 2014. Genetic and educational assortative mating among US adults. Proceedings of the National Academy of Sciences of the United States of America 111, 7996–8000.

Domingue, B.W., Belsky, D.W., Conley, D., Harris, K.M., Boardman, J.D., 2015. Polygenic influence on educational attainment: new evidence from the National Longitudinal study of adolescent to adult health. AERA Open 1 (3), 1–13.

Feldman, M.W., 1971. Equilibrium studies of two locus haploid populations with recombination. Theoretical Population Biology 2, 299–317.

Feldman, M.W., Cavalli-Sforza, L.L., 1976. Cultural and biological evolutionary processes, selection for a trait under complex transmission. Theoretical Population Biology 9, 239–259.

Feldman, M.W., Aoki, K., Kumm, J., 1996. Individual versus social learning: evolutionary analysis in a fluctuating environment. Anthropological Science 104, 209–213.

Feldman, M.W., Christiansen, F.B., Otto, S.P., 2013. Gene-culture coevolution: teaching, learning, and correlations between relatives. Israel Journal of Ecology and Evolution 59, 72–91.

Fogarty, L., Strimling, P., Laland, K.N., 2011. The evolution of teaching. Evolution 65, 2760–2770.

Fogarty, L., Wakano, J.Y., Feldman, M.W., Aoki, K., 2015. Factors limiting the number of independent cultural traits that can be maintained in a population. In: Mesoudi, A., Aoki, K. (Eds.), Learning Strategies and Cultural Evolution during the Paleolithic. Springer, Japan, pp. 9–21 (Chapter 2).

Hamilton, W.D., 1964. The genetical evolution of social behaviour. I. Journal of Theoretical Biology 7, 1–16.

Hewlett, B., 2013. "Ekeloko" the spirit to create—innovation and social learning among Aka adolescents of the central African rainforest. In: Akazawa, T., Nishiaki, Y., Aoki, K. (Eds.), Dynamics of Learning in Neanderthals and Modern Humans, Cultural Perspectives, vol. 1. Springer, Tokyo, pp. 187–195.

Hewlett, B.S., Cavalli-Sforza, L.L., 1986. Cultural transmission among Aka pygmies. American Anthropologist 88, 922–934.

Hewlett, B.S., Fouts, H.N., Boyette, A.H., Hewlett, B.L., 2011. Social learning among Congo Basin hunter-gatherers. Philosophical Transactions of the Royal Society B 366, 1168–1178.

Hoppitt, W.J.E., Brown, G.R., Kendal, R., et al., 2008. Lessons from animal teaching. Trends in Ecology and Evolution 23, 486–493.

Kendal, J., Giraldeau, L.-A., Laland, K., 2009. The evolution of social learning rules: payoff-biased and frequency-dependent biased transmission. Journal of Theoretical Biology 260, 210–219.

Kobayashi, Y., Wakano, J.Y., Ohtsuki, H., 2015. A paradox of cumulative culture. Journal of Theoretical Biology 379, 79–88.

Lehmann, L., Aoki, K., Feldman, M.W., 2011. On the number of independent cultural traits carried by individuals and populations. Philosophical Transactions of the Royal Society B 366, 424–435.

Lehmann, L., Feldman, M.W., 2009. Coevolution of adaptive technology, maladaptive culture, and population size in a producer-scrounger game. Proceedings of the Royal Society B: Biological Sciences 276, 3853–3862.

Lehmann, L., Wakano, J.Y., Aoki, K., 2013. On optimal learning schedules and the marginal value of cumulative cultural evolution. Evolution 67, 1435–1445.

Maynard Smith, J., 1978. The Evolution of Sex. Cambridge Univ. Press, Cambridge UK.

Nakahashi, W., 2015. The evolution of culturally transmitted teaching behavior. In: Mesoudi, A., Aoki, K. (Eds.), Learning Strategies and Cultural Evolution during the Palaeolithic. Springer, Tokyo, pp. 23–33.

Premo, L.S., 2015. Mobility and cultural diversity in central-place foragers: implications for the emergence of modern human behavior. In: Mesoudi, A., Aoki, K. (Eds.), Learning Strategies and Cultural Evolution during the Palaeolithic. Springer, Tokyo, pp. 45–65.

Premo, L.S., Scholnick, J.B., 2011. The spatial scale of social learning affects cultural diversity. American Anthropologist 76, 163–176.

Rietveld, C.A., Conley, D., Eriksson, N., et al., 2015. Replicability and robustness of genome-wide-association studies for behavioral traits. Psychological Science 25, 1975–1986.

Rogers, A.R., 1988. Does biology constrain culture? American Anthropologist 90, 819–831.

Strimling, P., Sjöstrand, J., Enquist, M., Eriksson, K., 2009. Accumulation of independent cultural traits. Theoretical Population Biology 76, 77−83.

Takakura, J., 2013. Using lithic refitting to investigate the skill learning process: lessons from Upper Paleolithic assemblages at the Shirataki sites in Hokkaido, northern Japan. In: Akazawa, T., Nishiaki, Y., Aoki, K. (Eds.), Dynamics of Learning in Neanderthals and Modern Humans, Cultural Perspectives, vol. 1. Springer, Tokyo, pp. 151−171.

Tomasello, M., 1999. The human adaptation for culture. Annual Review of Anthropology 28, 509−529.

Uyenoyama, M., Feldman, M.W., 1981. On relatedness and adaptive topography in kin selection. Theoretical Population Biology 19, 87−123.

Uyenoyama, M., Feldman, M.W., Cavalli-Sforza, L.L., 1979. Evolutionary effects of contagious and familial transmission. Proceedings of the National Academy of Sciences of the United States of America 76, 420−424.

Wakano, J.Y., Aoki, K., 2006. A mixed strategy model for the emergence and intensification of social learning in a periodically changing natural environment. Theoretical Population Biology 70, 486−497.

Wakano, J.Y., Aoki, K., Feldman, M.W., 2004. Evolution of social learning: a mathematical analysis. Theoretical Population Biology 66, 249−258.

Wakano, J.Y., Miura, C., 2014. Trade-off between learning and exploitation: the Pareto-optimal versus evolutionarily stable learning schedule in cumulative cultural evolution. Theoretical Population Biology 91, 37−43.

Chapter 19

Multiple Origins of Agriculture in Eurasia and Africa

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INTRODUCTION

The history of human technological evolution is dotted with inventions and innovations. Some failed, others succeeded. The emergence of an agro-pastoral economy in a few regions was successful, apparently being the most influential revolutionary process in world history, a fact that did not escape the attention of the people several millennia ago. The Biblical story of the expulsion from the Garden of Eden is a known example, but similar notions were conveyed by early Egyptian, Greek, and Roman mythologies. Interestingly, three goddesses were considered responsible for the change through the introduction of cereals and fruit-tree farming. These were Isis in Egypt, Demeter in Greece, and Ceres in Rome (Harlan, 1992). Comparable tales were recorded in China and the Americas, though sometimes they are male gods. However, as far as science is concerned, it was only during the 19th century that scholars began to directly address the research issues that face us today. Alphonse de Candolle (1884) in the introduction to his seminal volume on the "The origins of cultivated plants" states that "in the progress of civilization the beginnings are usually feeble, obscure and limited … Between the custom of gathering wild fruits, grain and roots and that of regular cultivation of the plants which produce them, there are several steps" (1884, p. 2, English translation). Being familiar with ethnographic records concerning foragers' behavior, he mentions the example of the Australians and the Patagonians that if they do not consider vegetal resources "productive and easy to rear, they do not entertain the idea of cultivating them" (1884, p. 2, English translation). He then considers the question of the transfer of cultivated plants from one region to the other and indicates that adaptation is faster on the continents rather than on the islands. Having been one of four generations of Swiss botanists de Candolle knew about the "Colombian" exchange and how wheat, maize, millet, sweet potatoes, and other staples were widely diffused across the continents even prior to known historical records. In brief, de Candolle was fully aware of the questions posed by investigators since the early excavations of farming communities, known as the Neolithic Age, concerning the when, how, and why cultivation, horticulture, and animal domestication evolved.

The answers to each of these queries posit a different kind of challenge. The most difficult is why it happened after more than two or three million years of human evolution. Current answers refer to two options, namely, the "pull" and the "push" models (eg, Diamond, 1997; Bellwood, 2005; Gept, 2014). The first considers human desire to improve the standard of living as the main trigger. The second takes into consideration demographic pressure due to the rising size of human population and the demand for supplies as the causal reason. I will return to this issue in the final discussion after presenting the known evidence.

A little less complex topic is when it happened. This aspect seems the easiest to resolve. We can trace the "domestication syndrome" of plants and animals, due to the fast development of ^{14}C radiocarbon dating technique. Readings are given today as calibrated before present (cal BP) calculated on the basis of dendrochronology and other records of annual accumulations (eg, Brock et al., 2010; Taylor and Bar-Yosef, 2014). The best samples for dating, obtained through systematic excavations, are the short-lived seeds of annual plants and animal bones. Human skeletal remains come next while wood charcoal would be the last due to the possible effects of "old wood," the

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00019-3

remains of firewood collected by humans or of wooden posts employed for building.

The issue of where the transition from foraging to farming took place is debated due to the difficulty of identifying the nature and the dates of early cultivation, already practiced by hunter-gatherers during the Terminal Pleistocene and Early Holocene. Only rarely did early experiments result in the establishment of fully agricultural societies. Domesticated animals and plants were transferred from the original core areas of domestication to other regions and were adopted therein by locals who sometimes initiated cultivation of local plants that became domesticated through time.

The pioneering studies to discover the origins of plant domestications were conducted during the early 20th century by N. Vavilov, a Russian botanist who identified nine megacenters in Eurasia, Southeast Asia, New Guinea, and Meso- and South America where he recognized the presence of wild species that later became domesticated (Vavilov, 1926). J. Harlan rejected the simple approach of Vavilov and instead followed de Candolle's idea that current and past information on plants, uncovered through archaeological investigations, should be taken into account in tandem with human activities during the past millennia (Harlan, 1971, 1992, 1995). On the basis of the available information he suggested to geographically identify "centers" and "noncenters," thus pointing to the Near East (or the Fertile Crescent) as a center while Africa (across the Sahel and in Ethiopia) was a noncenter; to North and South China as centers but Korea, Japan, Southeast Asia, and the Pacific as noncenters. Mesoamerica was considered as a center and South America as a noncenter. The noncenters were in the receiving ends of the dispersals of humans and staple food plants (Fig. 19.1). Later, north of South America and the Andes were added to the list of centers (eg, Diamond, 1997, 2012; Piperno and Pearsall, 1998; Bellwood, 2005; Purugganan and Fuller, 2009; Zohary et al., 2012; Gept, 2014). Once domestication of plants and animals happened in these centers, all scholars agree that people, products, techniques, and oral information were transmitted to other places. In the noncenters, additional domestication took place (Fig. 19.1). On the whole, during the last two decades the amount of data concerning the domestication of plants and animals increased rapidly and continues to do so. For brevity, this review will relate only to the formative phases of agricultural systems, at the time of the Terminal Pleistocene and the first half of the Holocene, approximately from 23,000 to 8000 years ago. To clarify matters, I will first deal with the current terminological conundrum followed by the information concerning prehistoric social contexts within which the onset of plant cultivation and animal domestication took place. This will lead us to animal domestication that is a simpler subject to follow than the processes involved in plant domestication. Finally, selected brief regional surveys of Eurasia and Africa and a shorter one for

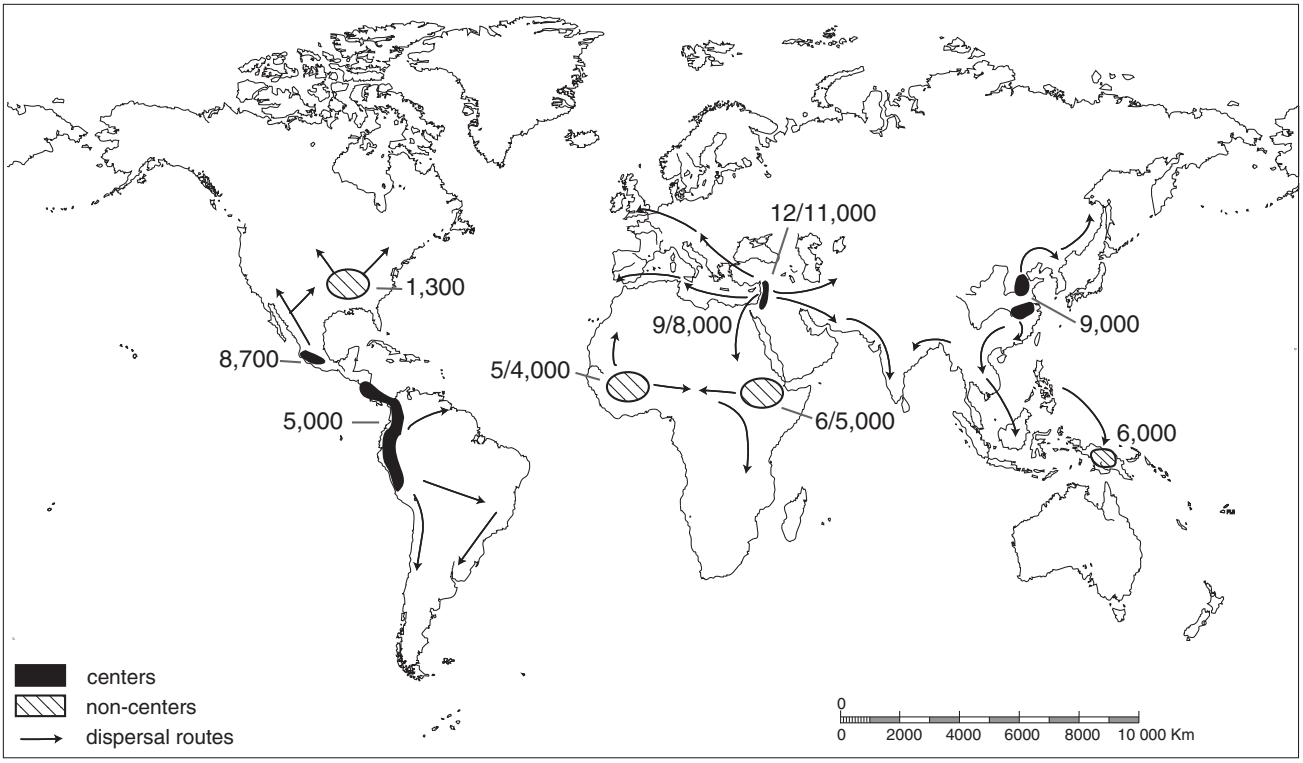

FIGURE 19.1 Centers and noncenters in the world with the approximate date for early cultivation of staple crops.

the Americas will exemplify the various pathways by which the initiation and early development of agricultural systems occurred. The discussion will summarize current hypotheses concerning the emergence of agro-pastoral societies.

THE TERMINOLOGY CONUNDRUM

Before delving into presentations of data and interpretations, we should briefly pay attention to the terms used in this chapter as in numerous previous publications. D. Harris (2007, p. 17) correctly noted that the academic discourse employs terms, such as "agriculture," "cultivation," "domestication," "horticulture," and "pastoralism" that have multiple meanings, without further explicit explanations. The most problematic term is agriculture. The reasons for this are that the subject is of multidisciplinary nature and directly relates to the notion of food production. A great number of scholars interested in the origins of agriculture are trained in different disciplines such as archaeology, plant and animal sciences, economy, behavioral sciences, and paleoclimatology, within which this term implicitly bears different meanings. It seems that archaeobotanical evidence and plant paleogenetics clearly indicate that cultivation by hunter-gatherers occurred in different environments at different times across the continents, but not everywhere. It resulted with the domestication of the current staple food only in the centers, and was adopted in the noncenters (Harlan, 1971, 1992; Diamond, 1997, 2012; Gept, 2014).

Animal domestication took place in several geographic environments but the most common suppliers of meat to be domesticated, namely, wild goat, sheep, cattle, and pigs, are to be found in Asia (eg, Zeder, 2012, 2015; Marshal and Weissbrod, 2011; Marshall et al., 2014). Apparently, early plant cultivation that is in some areas referred to as agriculture or plant management was practiced by semi-sedentary or fully sedentary societies and was not necessarily accompanied by animal husbandry (eg, Denham, 2011). The state of reduced mobility characterizes foraging groups in particular regions since the Late Pleistocene and is indicated, for example, in the Levant by the presence of commensals such as the dog, the house mouse, spiny rat, and house sparrow (eg, Tchernov, 1991; Auffrey et al., 1989; Wayne and vonHoldt, 2012; Larson et al., 2012; Zeder, 2012). Should these groups be called "affluent foragers" or simply "complex societies of hunter-gatherers"? Current literature uses both terms (eg, Crawford, 2011).

The cumulative results of the evolution of plant cultivation and eventual domestication became the socio-economic tipping point in humankind's history taking place at different times across all continents, except for Australia. What is referred to currently as the "agricultural revolution" was almost a century ago labeled by V.G. Childe as the "Neolithic revolution," a periodic term borrowed from the research of Stone Age archaeology (Lubbock, 1865). Childe (1929, 1952) correctly considered the economic changes that took place during the Early Holocene (the last phase of the Quaternary) within the social context of Southwestern Asia as a major evolutionary step. It later led to the formation of the tern Neolithization as the overall process for the emergence and adoption of plant framing and animal husbandry by Old World societies.

Recently, given the cumulative environmental impacts of agricultural and industrial societies during the last 11 millennia, geologists and climatologists adopted the term Anthropocene as a replacement for the term Holocene to stress the impact of humans on planet earth. However, the historical reality is that cultivation began in numerous areas long before the end of the Pleistocene while in other regions several millennia after the onset of the Holocene. Indeed, the intense impact of humans on the planet began in certain regions earlier than in others. We note that generalizations, common in our historical interpretations, tend sometimes to obscure the detailed regional evidence. Thus a senior geoarchaeologist indicates the caveat in employing this terminology by stating that the use of "Anthropocene … revolves around the increasingly salient role of cultural agents that selectively shape a multitude of small and large specific areas, so as to favor divergences and disjunctures … and … the result is a nonnormative dynamic of changing spatial configuration and temporal scales that was superimposed on noncultural Holocene processes predominantly steered by 'natural' forces" (Butzer, 2015, p. 1539). He argues that "flexible, time-transgressive concept, rather than a firm time-frame, should stimulate identification and investigation of centers of early or unusual human disturbance" (Butzer, 2015, p. 1539). Differences between geographic regions will be given further attention in the following pages.

All scholars agree that the genetic changes in plants and animals caused by active human intervention referred to as the domestication syndrome, originally defined by Hammer (1984), occurred at different times. An approach that views the process as gradual identifies three phases in plant domestication: (1) gathering, when people collected wild annual plants in the environment; (2) cultivation, when wild plant genotypes were systematically sown in fields of choice; and (3) domestication, when domesticated-type mutant plants were grown annually (Weiss et al., 2006). Several scholars prefer the primacy of the term domestication over agriculture, which is a bit vaguer but could be used for the times when the process of animal and plant domestication was reached and is evidenced through the archaeological remains of agro-pastoral economy, also referred to as fully agrarian societies (eg, Zeder, 2012, 2015). The archaeology of the Fertile Crescent provides a

wealth of archaeobotanical and archaeozoological details that suggest a general correlation in time between the cultivation of fully domesticated plants and livestock.

Numerous scholars see the evidence of cultivation by hunter-gatherers as falling under the categories of agriculture or agronomy (eg, Yen, 1989). Documents describing the activities of native Australians, Americans, and Africans demonstrate that to protect and enhance the production of their vegetal sources they engaged in cultivation actions (eg, Harlan, 1992). For example, Australians diverted water to flood forests in the dry season, constructed water-spreading devices, and more. There are ethnographic records of the 19th century describing foragers' activities, which could have been the results of previous contacts with fully agricultural societies such as the introduction of the taro (*Colocasia esculenta*) into Arenham land in Northern Australia (Jones and Meehan, 1989). When sedentary lifeways evolved in California, acorns became the most important staple food as shown by the increase of milling stones (Stevens and McElreath, 2015).

In sum, in order not to be entangled by the ambiguities of the general terms employed by various researchers I herewith employ "cultivation" as a descriptive expression when the archaeological evidence demonstrates repeated annual sowing of seeds and collection of the ensuing harvests. Fields could be wetlands, cleared areas by fire or other techniques, subject to tillage, digging channels for water, and more, while the plants were not necessarily fully modified genetically. Acceptance of the evidence of plant domestication is based on the documented archaeobotanical evidence (eg, Zohary et al., 2012; Fuller, 2011; Fuller et al., 2011 Crawford, 2011; Smith, 2011; Lee, 2011; Denham, 2011). However, whether the transition from cultivation of wild species to fields with fully domesticated plants was a short or a long process (a few centuries or more than a millennium) is a controversial issue. It will be discussed later in the section on the Levant (see section The Centers for Plant Cultivation and Domestication).

THE SOCIAL CONTEXTS OF CULTIVATION AND DOMESTICATION EMERGENCE

The onset of cultivation and animal domestication that changed the course of human evolution began in the social context of semisedentary or sedentary hunter-gatherers. The most intriguing issue is why foragers who were better off as Paleolithic mobile groups became sedentary. The question can be phrased also as "why cultivate?" (Barker and Janowski, 2011).

Sedentism is a cyclical phenomenon that could have taken place during different times in the course of the Paleolithic period (Bar-Yosef, 2001). The choice to become sedentary or return to a mobile way of life expresses the nature of human ability to manipulate their environment while being fully aware, probably not always, of changes caused by their behavior. We notice these changes in making variable decisions through archaeological investigations when most regions of the world became inhabited after the Late Glacial Maximum (LGM, c. 24-19/18 ka cal BP; eg, Cohen, 2011 and references therein). Limitations on free movement, fear of disrupting their mating systems, the developing sense of "territoriality" in view of competition with other groups, and so forth, enforced certain restrictions on annual movements among lower and middle latitude foragers. Anticipated mobility meant seasonal moves and the emergence of places that were repeatedly occupied over the years. In some but not necessarily all localities, humans built huts and later houses, and used storage facilities that were not always recoverable in the excavations (eg, baskets). Seasonally inhabited localities were the context where human garbage, due to reduced mobility, resulted in the formation of rich dumps that attracted the gray wolf, the ancestor of the dogs, as well as other commensals. Good examples are the Natufian hamlets in the Levant (c. 14,500−11,700 cal BP) that created the conditions for commensals such as the dog, house mouse, spiny rats, and house sparrow (Tchernov, 1991; Tchernov and Valla, 1997; Zeder, 2012). Similar sedentary and semisedentary villages are reported from other parts of Asia (China, Korea, and Japan) and will be discussed later in this chapter.

While sedentism or semisedentism, and anticipated mobility between two habitats, provides advantages for females and children due to the reduction of residential moves, it also means the acceptance of territorial limitations. Under such circumstances foremost is the need to have a buffering strategy in case of a decrease in resources caused by minor shifts of annual climate (eg, several years of repeated droughts or very harsh winters). Experiments in cultivation could have been done under improved climatic conditions and supply the surplus needed for bad seasons or bad years. Humans are known for their foresight (eg, Jempa et al., 2012) and particular resilience in resolving complex situations caused by abrupt climatic changes. It is therefore surprising why they became cultivators when they could only intensify their subsistence techniques or move to other areas, a question posited by different scholars (eg, Diamond, 1997, 2012; Bellwood, 2005, 2013; Barker and Janowski, 2011; Zeder, 2015). In brief, one proposal is to see cultivation and animal domestication as a response to worsening climatic conditions in a situation of restricted mobility incorporated, as mentioned earlier, in the push models. The alternative view, labeled as the pull models, suggests that the initiation of cultivation emerged from the availability of stable wild food resources and human innovation targeted to improve their exploitation. Without deciding on which of the two hypotheses is presently

correct, examining the variability of past human interactions with their immediate environments is required. Information gathered for testing the optimal foraging models demonstrated that they help understand the observed variation in the diets of Paleolithic hunter-gatherers (eg, Kelly, 2013). However, in the current database there are specific exceptions such as taboos of hunting or eating a particular organism, as well as symbolic signaling in the hunting of large mammals (Speth, 2010). There are similar examples concerning plants but only one is mentioned here, the sacred relationship involving rituals related to oak trees in California (Harlan, 1992) or forests in the Himalaya (Negi, 2010).

Returning to the basic question of "why" cultivate, frequently the answer is that intensification of resource exploitation was not sufficient for foragers who established permanent hamlets or anticipated seasonal moves between locations across the landscape. Temporary solutions included experiments in growing plants. Apparently systematic cultivation of wild plants could be simply a matter of personal choice. Inventions and innovations during human evolution either succeeded or failed. There is no consensus on how those were accepted or rejected by past societies. Models demonstrate that larger populations increase the probability of adoption of innovations (eg, Shennan, 2000). However, testing these models with material culture of ethnographically recorded hunter-gatherers produced mixed results (eg, Collard et al., 2013 and references therein). Under annually unstable climatic conditions the choice to cultivate falls within the efforts to intensify food security in "good times" with the foresight of expecting the "bad times." Apparently, this is what took place among mobile and later by sedentary hunter-gatherers as indicated by the archaeological data, and exemplified later in this chapter.

World population growth could have never taken place without the contribution of domesticated plants and animals to human diet. It would be logical to start and discuss this by first presenting the information about plants, given the dietary contributions of starch from cereals or roots and protein from legumes. However, the accumulated knowledge concerning animal domestication is better known and the interpretations by archaeozoologists, palaeogeneticists, and researchers of animal behavior are currently better structured than the interpretations concerning plant domestication.

ANIMAL DOMESTICATION

The reasons for better knowledge about animal remains are undoubtedly due to the results of the archaeological excavations where bones are generally better preserved than seeds. This is why several decades ago the concept of "Man the Hunter" got primacy over "Woman the Gatherer" (eg, Lee and DeVore, 1968; Dahlberg, 1981). The analysis of animal bone assemblages from Paleolithic excavations was impacted by the ethnographic research of L. Binford who questioned the earlier accepted interpretations concerning hunting and meat consumption (Binford, 1981). Recent discoveries indicate that the composition of human diet as documented by ethnographic studies resembles that of the past. In the semitropical to mid-latitudes of both hemispheres vegetal sources constitute up to 50–70% of the diet (eg, Kelley, 2013). The rate of meat consumption increases considerably toward the higher latitudes and fish and shellfish along ocean shores. Yet the better bone recovery resulted in a better understanding of the multistage process that led to the intensification of human–animal relationships and ended with a better understanding of animal domestication (eg, Vigne et al., 2011; Vigne, 2011, 2015; Zeder, 2011, 2012, 2015; Ottoni et al., 2013; Marshall et al., 2014).

In brief, animal domestication is characterized by diverse phenotypic and behavioral changes including increased sociality, earlier reproduction that is often controlled by humans, genetic isolation from wild progenitors, as well as modifications of the endocrine and metabolic systems. We know today the end of the process, as well as when animals became feral or were not fully isolated from interbreeding with their wild relatives. The various stages from the onset of the domestication process are viewed through studies of the bone assemblages recovered in numerous sites and paleogenetic investigations.

The process of domestication of four animal species in Southwestern Asia is based on the archaeological sequence where goat, sheep, pig, and cattle became the sources of meat, fur, hides, hair, wool, bones, horn cores, and later, milk (Vigne et al., 2011; Vigne, 2015; Zeder, 2012; Evershed et al., 2008). This evolutionary sequence began with commensalism that triggered the control of wild animals and their captivation, leading to extensive and intensive breeding, and the final addition of pets, such as cats. The continuous, geographically determined, gradual domestication of those four animals is classified by Zeder (2012, 2015) as the expression of three different pathways although they were partially sequential. These are the "commensalism," "prey," and "directed" pathways. In each of them there is a role for transformations in the nature of the domesticator and the domesticated, namely interactions beyond the common mutualism in the natural world (Zeder, 2012, p. 163). Marshall et al. (2014) hold a similar view but stress the complicated relationships of gene flow between the managed and wild animals, and indicate differences that stem from the cultural background of diverse societies.

Each of the steps in the sequence of animal domestication occurred within a social context uncovered through

archaeological excavations. It was a coevolutionary process during which animals adapted to a niche controlled by humans who in accordance changed their behavior. The evidence for the in-tandem changes are not always well recorded although the retrieval of archaeozoological evidence allows for the documentation of paleogenetics of the domesticated species. In addition, structural arrangements within the villages, animal dung, evidence of tuberculosis, and infections by parasites, portray some of the results of this coevolution process (Herskovitz et al., 2008; Baker et al., 2015; Le Bailly et al., 2003, 2005).

The example recognized by all authorities for an early behavioral evolutionary process is the "commensalism," a compassionate type of animal–human interaction which predates later domestication. It involves dogs, ie, the domesticated gray wolf (*Canis lupus*), serving as partners in hunting, guarding, and as pets, and in later millennia in East Asia also as food (eg, Lindblad-Toh et al., 2005; Larson et al., 2012). The attraction of the wolves to human garbage is considered as the reason for the original association. Such a situation in Paleolithic times would occur when foragers' mobility considerably decreased, probably to just two locations that portray their anticipated seasonal movements. Stable semipermanent camps, whether of a small or a larger group would create an ideal location for commensalism. Frequently cited evidence are the fossil dogs uncovered in Natufian sites in the Levant (Davis and Valla, 1978; Tchernov and Valla, 1997). However, the debate concerning the timing and the original location(s) of dog domestication is still ongoing (eg, Savolainen et al., 2002; Galibert et al., 2011; Larson et al., 2012; Skoglund et al., 2015). The earliest chronological estimate to when dogs became partners of hunter-gatherers is generally seen as the Late to Terminal Pleistocene (Skoglund et al., 2015). In addition, the process itself involved human constant intentional selection as the selection done by D.K. Belaev and his followers while taming and domesticating the silver wolf (Trut et al., 2009).

Many millennia elapsed between dog domestication and the intense human–animal relationships that began during the Early Holocene with the domestication of goat, sheep, cattle, and pig in Southwestern Asia, and pig in East Asia. Added later to the repertoire of domesticated animals were reindeer (North Europe), llama (South America), water buffalo (South and East Asia), zebu (India), donkey (Africa), and camelids and yak (Asia and South America). All these were seen as legitimate prey targets by hunter-gatherers but were suitable to become domesticated due to their particular pattern of behavior.

Wild sheep (*Ovis aries*) and bezoar (wild goats, *Capra aegagrus*) are herd animals and were hunted in the Levant during many millennia. It was a change in the intentions of hunters that instead of getting immediate returns by killing, they encircled and controlled small groups of goats and sheep ending up in management including culling young males and keeping the females and the kids. Continuous control in pens and involvement in breeding and selection facilitated the growth of herds in the villages. Herding in pastures away from the village enabled gene exchange between the domesticated *Capra hircus* and the wild bezoar (Naderi et al., 2008). The mtDNA data of domesticated goats and bezoars indicate that the domestication could have occurred in two locations: the Northern Levant (sometimes mistakenly referred to as Eastern Anatolia) and the Zagros mountains. However, as the earliest Neolithic villages were in the former region and other contemporaneous settlements were within easy access through the Tigris River and its Mesopotamian tributaries, the most parsimonious explanation is that transmission and ensuing imitation of innovative approaches between centers and noncenters played here a decisive role (Zeder, 2012, p. 175).

Archaeological evidence retrieved from villages in Southwestern Asia suggests that wild boars (*Sus scrofa*) were attracted to and opportunistically exploited the dumps around sedentary settlements of early farmers (eg, Ervynck et al., 2001; Zeder, 2011). Within a context of a new kind of commensalism keeping piglets was possibly the first step leading to domestication. In the same geographic area sedentary foragers at Hallan Çemi, on the bank of a tributary of the Tigris River, may have tried the same approach (Redding, 2005). The assemblage from the central activity area of this site is dominated by female pigs indicating that this was either a failed experiment in domestication or a ritual slaughter, as the rest of the faunal assemblage reflected a regular hunting profile (Starkovich and Stiner, 2009).

Morphological comparisons between wild and domesticated pigs are considered as the best example for the resulting biological changes. Skulls of domesticated pigs are reduced to one-third of that of their ancestors. Similar brain reduction occurred among other mammalian species as well as in birds and fish (Zeder, 2012 and references therein). A comparable process of pig domestication occurred in China in the context of Early Neolithic villages (Larsen et al., 2010). Given the as yet limited information it seems that the pioneering farmers were those who grew the millet in the Yellow River basin from which pigs were dispersed further south into the Huai River basin and the Yangtze River basin, respectively (Yuan and Flad, 2002; Fig. 19.5).

According to the zooarchaeological studies cattle was domesticated in the same geographic area of the Northern Levant. Given the size and strength of the wild progenitor (*Bos premigenius*) it is not surprising that it became an important element in rituals and symbolism, as evidenced by the well-known presentations of bucrania (cattle skulls), first found in Early Neolithic villages in the Levant but best

known from the houses of Çatalhöyük (Hodder, 2007). The results of cattle domestication, similarly to those of other species, caused size changes (eg, reduction in the sexual dimorphism). Milk production is directly associated with cattle breeding. The evidence is derived from $\delta^{13}C$ values of the major fatty acids of milk fat recovered from a large number of pottery vessels (Evershed et al., 2008). Archaeologically, the earliest use of milk was found in sites that date to the ninth millennium cal BP in Western Anatolia and the margins of Southeast Europe and was later traced in pottery from the Levant. The dispersal of the goat, sheep, and cattle from Southwestern Asia resulted in milk consumption in Europe, North Africa, Egypt, Sudan, Ethiopia, and across the Sahel. Lactose tolerance after weaning is an exclusively epigenetic human trait made possible by the continued production of the enzyme lactase into adulthood. Genetic studies demonstrated lactase persistence is also present in India and is generally distributed in a northwest to southeast trajectory of this subcontinent (Gerbault et al., 2011; Gallego Romero et al., 2011). Dairy products were produced later and evidence for cheese in northern Europe first appeared around 7400 cal BP (Salque et al., 2013).

During the second half of the Holocene (after 8000 cal BP) other livestock were domesticated including the wild water buffalo (*Bubalus arnee*) in Southeast Asia and the wild yak (*Bos mutus*) in Tibet, for which the exact age is yet unknown. Through the same process draft animals were domesticated after 6000 cal BP and even later as reported from various regions of Asia. These included horses (*Equus caballus*), the double-humped Bactrian camel (*Camelus bactrianus*), and finally the one-humped Arabian camels (*Camelus dromedarius*). The exception is the case of the donkey (*Equus asinus*) domestication that occurred in Africa (Marshall et al., 2014). All these draft animals were on the faunal lists of hunter-gatherers and were even later hunted by farmers. Current hypotheses link their domestication to the evolving trade networks between the emerging Bronze Age civilizations in the different geographic areas of Asia (Mesopotamia, Bactria, India, and China). However, we cannot exclude the alternative interpretation that the horses and the Bactrian camels already served as means of transportation between farming centers and noncenters during the early sixth millennia cal BP.

The more interesting case is that of the donkey whose natural distribution was across the Sahara to the eastern foothills of the Atlas mountains (Kimura et al., 2011; Fig. 19.1). According to current research they were hunted and later domesticated in the arid or semiarid habitats in eastern Sahara, the Red Sea Hills, the Nile Valley, and Somaliland, which is supported by the genetic analysis of Nubian and Somaliland donkeys (Kimura et al., 2011; Marshall et al., 2014). While according to the genetic evidence they are mitochondrially distinct, chronologically the Nubian donkeys were possibly domesticated in the Eastern Sahara by 8900–8400 cal BP. Apparently, like in the case of the plants (see later), the domestication of donkeys could have been done by foragers who adopted farming from the "foreigners" who migrated from Southwest Asia into East Africa via Egypt. The current genetic evidence indicating such migration of farmers suggests that donkey domestication coincides with the introduction of plants by migrants who arrived some 8000 years ago (eg, Gallego Llorente et al., 2015). An additional suggestion for a migration from Southwest Asia reaching the Horn of Africa (Hodgson et al., 2014) is based on extant human populations' genetics. It suggests dating the migration to the preagricultural time and ties it with Ethiopian-Somali ancestry and the diversification of the Afro-Asiatic languages.

PATHWAYS TO THE DOMESTICATION OF PLANTS

The course of plant domestication may resemble the course of animal domestication but human involvement in exploitation of vegetal resources was different in its nature and history. Plant food is consumed as a major source of calories by primates and its exploitation was a daily activity of hominins since the Early Plio-Pleistocene times (Ungar, 2007; Collins and McGrew, 1988; Wrangham et al., 1998). It is hard to trace human plant use in the archaeological records whether as a food source or for making tools, bedding, strings, baskets, constructing huts, and more. Ethnographic recording among open-forest dwellers in tropical and subtropical South America, Northeast India, New Guinea, and other regions demonstrated that vegetal substances make up a high percentage of the diet (eg, Kelly, 2013). Indeed, foragers in Southeast Asia and mainland China extensively used bamboo during the Paleolithic period yet left behind only assemblages of stone tools, fireplaces (in well preserved sites), and large collections of animal bones (Bar-Yosef et al., 2012). Still Pleistocene-age limited sources provided accidental discoveries in depositional contexts where plants were preserved. For example, edible plants retrieved through floatation at Gesher Benot Ya'acov (Jordan Valley, Israel) dated to some 780,000 years ago were associated with a few stone tools that indicated food processing (Goren-Inbar et al., 2002, 2014). It appears that waterlogged sites and lignite deposits provide the best environments for plant preservation (eg, the wooden spears from Schöningen; Thieme, 1997; Schoch et al., 2015). Additional information is obtained from Middle Paleolithic sites such as Kebara and Amud caves in Israel that exhibit the gathering of vegetal sources. Grass panicles identified through phytolith analysis in Amud (Madella et al., 2002) and a

considerable amount of wild legumes in Kebara cave (Lev et al., 2005). Evidence for exploitation of plants was discovered also in Paleolithic human calculus (Mariotti et al., 2015; Hardy et al., 2009; Henry et al., 2011).

With the expansion of archaeobotanical research in various geographic regions the retrieval of carbonized plant assemblages allows us to trace the first endeavors in cultivation. There is documentation of how foragers in several habitats between the lower and mid latitudes practiced wild plant cultivation. This change in human interactions with their environments occurred during the late Pleistocene and Early Holocene. In almost every region of the world hunter-gatherers experimented in growing edible plants and tending fruit trees (for details, see sections The Centers for Plant Cultivation and Domestication, The Spread of Agriculture to the "Noncenters" and Its Impacts, and Brief Review of the Americas). Yet, it is only in a few localities that cultivated plants became later the staple food such as millet, rice, wheat, barley, rye, maize, legumes, and the tropical tubers (Harlan, 1971, 1992; Diamond, 1997, 2012; Bellwood, 2005; Piperno and Pearsall, 1998). These are the centers.

Given the available information concerning the history of plant domestication I propose to identify several pathways by which foragers experimented with cultivation of wild plants and in rare cases, the domestication of animals (Eurasia and South America). The sequential activities that took place in the centers and resulted in the demographic growth that characterizes farming communities and emergence of agro-pastoral economies led to the distribution of languages (eg, Bellwood, 2013). Current archaeological examples, in spite of incomplete information, will illustrate the proposed classification of the different pathways. One characterizes the centers and three others the noncenters, identified as follows (Fig. 19.1):

Centers: Paleolithic hunter-gatherers who relied on predomesticated plants in providing a major portion of their diet began systematically to sow designated fields after clearing the natural vegetation, tilling, and harvesting every season. These activities took place in a context of hamlets or villages with rounded dwellings and private and public storage facilities. The pioneering cereal cultivators interfered with the natural growth in the fields by selecting plants with nonshattering rachis, a variant that occurs (though rarely) in wild stands. Dominance of the domesticated varieties, recorded in the studied charred archaeobotanical assemblages was achieved in about 1000 or 1500 years (Willcox, 2012; Zohary et al., 2012). Hypothetically employing an annual systematic selection of nonshattering ears could have shortened the process of domestication to some 30–200 years (Hillman and Davies, 1990; Abbo et al., 2012). The emergence of the fully agricultural package including domesticated animals occurred in the Fertile Crescent, North and South China (Cohen, 2011), Mesoamerica, and the Andes (Piperno, 2011).

Noncenters A: Foragers cultivated different wild plants but the arrival of domesticated species from a center enhanced the systematic growth of indigenous long-known plants that resulted in their domestication (eg, Diamond, 1997; Piperno, 2011). The introduction of domesticated animals had a similar impact. For example, such were the cases of Ethiopia and Somaliland where the domestication of finger millet (*Eleusine coracana*), the grass species *tef* (*Eragrostis tef*), sorghum (*Sorghum bicolor*), and others took place. In the western Sahel pearl millet (*Pennisetum glaucum*) was domesticated, an additional species in the forest–savanna habitats.

Noncenters B: Hunter-gatherers who started cultivating several plants and eventually domesticated a few, reached in some areas high population densities before one or several major staple food species arrived into their area. The introduction of these domesticates motivated the domestication of local animals or plants, ie, the pig in Europe or Azuki bean in Korea and Japan (eg, Larson et al., 2007; Lee, 2012)

Noncenters C: Foragers who relied on gathering wild plants adopted the newly introduced domesticated species and became farmers. There is ample evidence that gathering of local plants continued for centuries during the adoption of staples brought in by newcomers in Egypt, South Africa, and South America (eg, Bellwood, 2005, 2013).

Two models are currently advocated in the literature concerning the dispersals of the entire or the partial agricultural package by migrating humans, as well as by transmission of products and knowledge. One views the territorial expansion of growing populations of farmers, whether within a region or on a continental scale as the cause of establishing cultivation in areas mostly occupied by hunter-gatherers. The second hypothesis adopts the position that cultivation may have started independently by individuals in different regions at more or less the same time, referring to the centers of the Fertile Crescent, Mesoamerica, the highlands and lowlands of South America, and China (eg, Brown et al., 2008); some publications enumerate even more localities where cultivation had emerged. The assumption is that hunter-gathers knew the plants and at one point started cultivating them. Still no farming developed in California where acorns were the staple food (eg, Anderson and Wholgemuth, 2012; Stevens and McElreath, 2015). In addition, the proposal that "agriculture was impossible during the Pleistocene but mandatory during the Holocene" was based on paleoclimatic sequence of events that was more dramatic in the northern higher latitudes than in the middle, subtropical latitudes (Richerson et al., 2001). In the latter region,

cultivation began before the onset of the Holocene while in other regions it happened only during the Early and even Late Holocene.

One of the main reasons for the confusion of what happened is caused by the overarching geographic definition of the centers, as defined by many scholars (eg, Harlan, 1992; Diamond, 1997; Bellwood, 2005). The area of these centers is too large in terms of square kilometers and territories to be occupied by hunting and gathering groups that form a tribe. In addition, the archaeological records in the known centers and noncenters are not sufficiently detailed, lacking accurate archaeological data, and therefore leads to caution in accepting the idea that all presumably contemporary villages located in a given region began cultivating within a century or two. We need to recognize that it is only in limited areas where cultivation and animal domestication was initiated. Several evolved to become the centers where the domestication of the founder crops (eg, wheat, barley, rice, maize, and others) caused major economic and demographic changes. For example, the Levant, one of the best archaeologically, archaeobotanically, and archaeozoologically investigated regions in the world has an area of about 200,000 km^2 of various vegetation belts where cultivation could have started (Figs. 19.2 and 19.3). When the hundreds of available radiocarbon dates available for the different prehistoric cultures are considered it becomes obvious that the changes began in a restricted "core area" that encompasses only about 10% of the total surface of the Levant (eg, Lev-Yadun et al., 2000; Abbo et al., 2010, 2013; Bar-Yosef, 2014; Borrell et al., 2015). In addition, the current literature presents opposing views concerning how long it took for most plants in the fields to become domesticated, ie, exhibiting genetic traits such as nonshattering ears, lack of dormancy, increase in grain size, and more. I will return to this in the discussion (section The Centers for Plant Cultivation and Domestication).

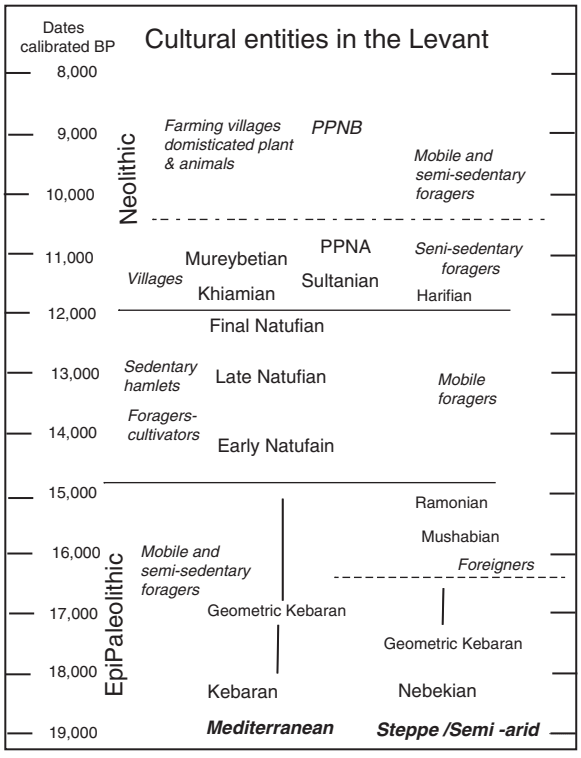

FIGURE 19.2 Time table of periods and cultures in the Levant mentioned in the text. All dates are calibrated before present (BP).

INTRA AND INTERREGIONAL CONNECTIONS

Before delving into the case studies of centers and noncenters in Eurasia and Africa, I will expand on the issue of long-distance connections, which are generally assumed but rarely discussed. In testing each of the hypotheses concerning dispersals or local inventions we need to examine the option of long-distance connections. A survey of optional ways reveals how the dispersals of the entire or the partial agricultural packages occurred across immense geographic regions. The issue of how people migrated, moved the products, replaced partially or entirely the local population as regards the "transition from foraging to farming" is better known from the European case. Even if we attribute it all to human migrations or immigrations, we still need to find out how this process occurred on land, by rivers, or by sea, as well as when did it happen, and how long it took for a new subsistence package to pass from the source areas, ie, the centers to the noncenters.

The best-known example is the move of farmers from Southwestern Asia into Europe as a process combining demic and cultural diffusion at the tempo, on average, of c. 1.3−0.7 km per year (Ammerman and Cavalli-Sforza, 1984; Fort, 2012). This complex process is now fully supported by paleo-genetics (eg, Pinhasi et al., 2005, 2012; Balaresque et al., 2010). The dispersal was by sea, along the Mediterranean coasts, by the Danube and the Rein rivers and by land. The time it took people to get across this continent, replace some local groups, and culturally impact others, is estimated through the use of radiocarbon dates (see section Europe and the Mediterranean Basin).

Ambiguities in radiocarbon dates due to the nature of the analyzed samples or gaps in the available records are sometimes taken to support the assumption that independent cultivation occurred even if localities were only 100 or 300 km apart. Evidence for independent experiments in cultivation is recorded among forages in many regions (see sections The Centers for Plant Cultivation and Domestication, The Spread of Agriculture to the "Noncenters" and Its Impacts, and Brief Review of the Americas). The Levantine example provides a contradictory conclusion when the sites are within the distance of one month's walk. The dispersal of cultivated plants such

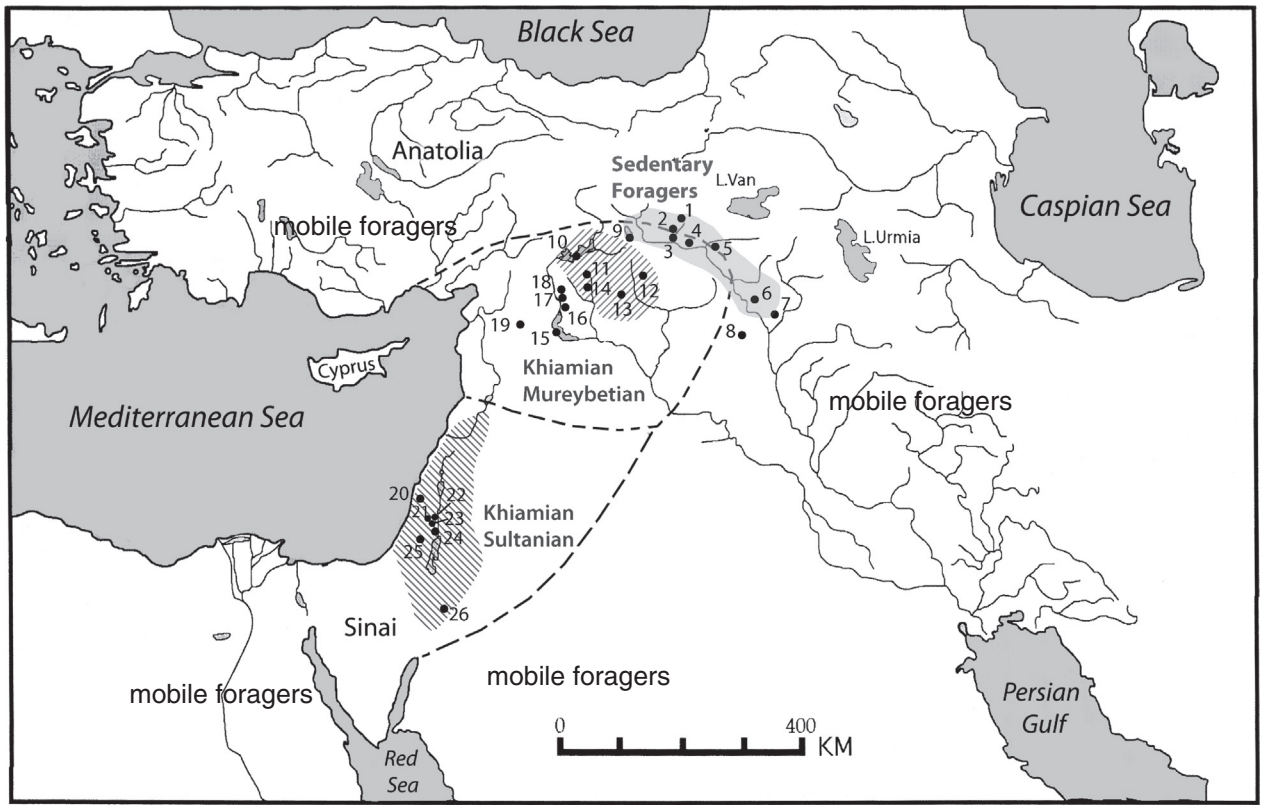

FIGURE 19.3 The geographic distribution of contemporary of mobile, sedentary foragers, and farming communities in the Levant. Paucity of field research is indicated by the blank area between the Northern and Southern Levant. The sites are: 1. Hallan Çemi; 2. Demieköy; 3. Körtik Tepe; 4. Hasankeyf höyük; 5. Gusir höyük; 6. Nemrik. 7. Mlefat; 8. Qermez Dereh; 9. Çayönü-round house; Göbekli Tepe culture(marked by parallel lines); 10. Nevali Çori; 11. Göbekli Tepe; 12. Karahan Tepe; 13. Sefer Tepe; 14. Sanilurfa Yeni Mahalle and Hamzan Tepe; The Euphrates farming villages: 15. Mureybet; 16. Jerf el-Ahmar; 17. Tel 'Abr 3; 18. Dka'ade, lower layer; 19. Tel Qaramel; Khiamina-Sultanian villages: 20. Nahal Oren; 21–23. Netiv Hagdud, Salibiya IX, Gilgal; 24. Jericho; 25. Motza; 26. Faynan16.

as wheat, barley, chickpeas, broad bean, and more from the Northern Levant to the southern region is indicated by the available radiocarbon dates. This conclusion is also supported by demonstrating that the transfer of animals over a distance 500–600 km from the core area to the Southern Levant was longer than for the plants and took some 500–1000 years based on dated bones of domesticated species in both regions (Martin and Edwards, 2013). In addition, the overland traditional walking routes in the Levant, such as "via *maris*" along the coastal plain and the "Kings road" along the Transjordanian plateau, were probably the routes that were used for importing Anatolian obsidian to the Southern Levant.

By boating on rivers (eg, the Tigris and the Euphrates) using simple vessels constructed of reeds and covered by hides, people could transport within a short time (a month or two) seeds, animals, technologies and information, from the "core area" in the Northern Levant into Mesopotamia. The Tigris River (1850-km long) and its tributaries were used as highways to reach the Zagros foothills and the margins of Southern Mesopotamia. Similarly, the Euphrates River (2800-km long) served both as means of interregional transmission of information and for the establishment of villages along a line of 80 km by members of the same Neolithic tribe (Willcox and Stordeur, 2012).

The move of domesticated plants and animals from the Levant into Central Anatolia and then to the shoreline of the Bosphorus straits before crossing to Europe was done along land routes as well as by baiting along the Mediterranean shores westward (Özdoğan, 2011; Arbuckle et al., 2014).

Moving to Southeast and East Asia we should note that the earliest seafaring across Sunda (the area of Southern China Sea) some 50,000–45,000 years ago, allowed hunter-gatherers to colonize by boats Sahul (the Pleistocene continent of New Guinea and Australia) and some of the neighboring islands.

Archaeological excavations on the island and in the Chinese mainland (Cohen, 2011) disclosed the colonization of Taiwan by Neolithic rice farmers, at the time that paddy fields were already developed, replacing the original population of hunter-gatherers. Later migrations by sea, known as the Austronesian dispersals, brought rice farmers and their languages to Southeast Asia, Melanesia, Micronesia,

and Polynesia (Bellwood, 2013). Observations made by archaeologists and linguists are supported by genetic evidence (Lipson et al., 2014).

The colonization wave by farmers from Southern China, reached Taiwan at about 6000 cal BP and by c. 4200 cal BP spread with domestic animals (pigs and chicken), rice, and pottery. It continued through the Philippines into Indonesia and the islands of the western Pacific. All these islands were originally inhabited by Paleolithic foragers and the new colonists either replaced or interbred with the local population. By c. 3500 cal BP they reached Guam and Western Polynesia (Tonga and Samoa), and by about c. 900 cal BP, Eastern Polynesia (Bellwood, 2013).

In sum, rivers, in every continent, served through the use of rafts, canoes, and boats, as prehistoric highways. Terrestrial movements took longer but the ability of humans to walk over long distances in most of the continents, and along valleys or coasts, should not be neglected in reconstructing dispersal routes. However, supportive archaeological evidence is required. Later, draft animals (eg, donkeys, horses, and camels) were also important means of transportation, at least in Eurasia and Africa, in particular during the second half of the Holocene.

THE CENTERS FOR PLANT CULTIVATION AND DOMESTICATION

Introduction

The examples presented earlier are sufficient to demonstrate that foragers in all centers cultivated and even domesticated plants and animals that in due course became an essential part of the current staple foods. Also in the noncenters, foragers cultivated plants and in several cases domesticated a few plants, but mostly adopted the incoming domesticated animals and founder staple crops. I now turn to the summaries of the centers and noncenters in Asia, Europe, Southeast Asia, and the islands as well as Africa, with a very brief review of the Americas. This choice is due to shortage of space.

Undoubtedly, among all the geographic regions, the Levant, the western portion of the Fertile Crescent, produced most of the relevant data due to numerous investigations that lasted for more than a century by various schools of archaeology (Gept, 2014). The richness of documentation from this region concerning plant and animal domestication led to the formation of more than one model explaining the origins of agriculture and its dispersal. In recent years, other regions yielded archaeobotanical remains retrieved from sedentary and semisedentary settlements of foragers and early farmers. There are also recent reports on animal exploitation and domestication in East Asia and the islands, Africa, Mesoamerica, Eastern North America, and South America. New techniques allow us to recognize shifts in human diets through the study of stable carbon isotopes, starch analysis of tools and grinding stones as well teeth calculus from prehistoric humans. As the amount of available information varies, and is scattered in many different journals and books, I will concentrate on the area that can provide support or challenge to the interpretations presented herein.

The Fertile Crescent

The Levant, a region located on the edge of the Eastern Mediterranean basin, features diverse topography. A 100-km cross-section in the southern subregion incorporates a coastal plain and a hilly area up to 1100-m above sea level covered by Mediterranean vegetation. A drop to 400-m below sea level characterizes the steppic Jordan Valley, up to the Jordanian plateau (c. 800 m above sea level) into a belt of Mediterranean vegetation and a slope into the Arabian desert. A longer section (c. 300 km) characterizes the Northern Levant that ends in the Northern Mesopotamian plain. Climate features winter precipitation and dry summers.

The LGM (25/24,000−19/18,000 cal BP) enjoyed in general high precipitation according to the record of the Dead Sea (Torfstein et al., 2013) but was interspersed by short drier fluctuations. Lower temperature, as demonstrated for the later Younger Dryas (YD, c. 12,800−11,700 cal BP), affected the Levantine biome and limited the geographic distribution of plant resources to the belts along the Mediterranean coast dominated by oak-pistachio forests and open parklands. Not surprisingly, Late Paleolithic mobile groups of hunter-gatherers, archaeologically recognized as the Kebarans and Nebekians, avoided the semiarid area (Fig. 19.2). Their occupations were found in the open parkland belt and oases, represented by the Ohalo II (and see later) and Kharaneh IV sites (Nadel et al., 2004; Maher et al., 2012). Those were clusters of small huts with fireplaces, grinding stones, rich microlithic tool-kits, bone tools, a few art items, and rare burials (Belfer-Cohen and Goring-Morris, 2011; Goring-Morris and Belfer-Cohen, 2011).

After c. 19,000 cal BP temperature began to rise, rainfall increased, and marginal semiarid belt became habitable. The mobile foragers, bearers of the Geometric Kebaran tool-kit spread all over the Levant (about 1000 km from north to south), whether through Mediterranean forests, parklands, or semiarid steppe. Around 16,500 cal BP the Mushabian and Ramonian hunter-gatherers, well trained in the exploitation of semiarid landscapes, invaded from Northeast Africa the Sinai peninsula and further north (eg, Bar-Yosef, 2011; Bar-Yosef et al., 2013; Garrard and Byrd, 2013). This period witnessed the contemporaneity of different tribes of foragers, resulting in interactions and

competitions for resources. A new population realignment possibly triggered by the short cold Heinrich 1 event led to the emergence of the sedentary or semisedentary Natufian culture (c. 15/14,500 through 11,700 cal BP). It flourished during the warmer Bølling-Allerød, and lasted through the YD that experienced changes in seasonal patterns, with wetter spells but colder than during previous millennia (Orland et al., 2012; Hartman et al., 2016).

A rare example of cultivation of wild cereals was discovered in Ohalo II, a waterlogged site near Lake Kinneret (Jordan Valley, Israel) that dates to c. 23,000 years ago. Several brush huts of foragers were exposed on an old shoreline, with interior beddings, rich stone and animal bone assemblages, a grinding stone, and a burial (Nadel et al., 2004). Near-perfect preservation allowed for the collection of over 150,000 plant remains. The cluster of the huts reflects most probably a sedentary community as indicated by the presence of commensals (house mouse and rat) and evidence of a year-round occupation encompassing seasonal plant gathering, hunting, trapping, and some fishing. A study of the cereals remains disclosed evidence for early cultivation of morphologically domestic-type cereals (Snir et al., 2015). That the cereals were prepared for consumption is supported by an analysis of starch residue retrieved from a large grinding stone, indicating processing of barley and oatmeal seeds (Piperno et al., 2004). The regression of Lake Kinneret at the time of occupation indicates a short dry climatic interval possibly triggering an experiment in cultivation of wild cereals in the local wetland. The prehistoric experiment resulted in the evolution of proto−wild weeds that generally grow in agricultural fields, appearing later as dominant plants in Early Neolithic sites from c. 11,700 through 10,300 cal BP (Snir et al., 2015).

Domesticated cereals are generally identified by smooth disarticulation scars on the rachises while the wild forms bear rough disarticulation scars. The presence of more than 10% of the domestic type in a given archaeobotanical assemblage is accepted as an indication for domestication. At Ohalo II, 36% of a total of 320 barley rachises show domestic-type scars, as well as 25% of the 148 wheat rachises. When taken together with the appearance of the proto-weeds the conclusion is that someone or the entire band practiced cultivation (Snir et al., 2015).

Unfortunately, there are as yet no additional information that would fall within the wider category of pre-domestication cultivation from c. 20,000 through c. 13,000 cal BP. In this context it is worth noting the interpretation of charred plant collections from Tell Abu Hureyra, on the banks of the Euphrates River, dated mostly to the time of the YD. The deposit-bearing Late Natufian material culture indicates predomestication cultivation of wild cereals and large-seeded legumes (Hillman et al., 2001). However, this claim has been refuted. The new interpretation of the archaeobotanical assemblage is seen as mirroring a change in gathering strategy that incorporated edible arable weeds such as rye before and during the YD (Colledge and Conolly, 2010). A different view, derived from the study of a Late Natufian plant assemblage from Dederiyeh cave (Fig. 19.2) west of Abu Hureyra, claims predomestication cultivation of emmer and einkorn wheat (Tanno and Willcox, 2012; Tanno et al., 2013; Ozkan et al., 2011).

These arguments reflect the importance ascribed to the Natufian culture and its role in various hypotheses concerning the theoretical aspects of the origins of agriculture (eg, Bellwood, 2005; Zeder, 2011, 2012; Asouti and Fuller, 2012; Fuller et al., 2012; Zohary et al., 2012; Abbo et al., 2013). Given the large number of papers, edited volumes, site reports, and book chapters dedicated to the role of the Natufian culture in the transition from foraging to farming only a few are cited here (eg, Cauvin, 2000; Bar-Yosef and Valla, 1991, 2013; Goring-Morris and Belfer-Cohen, 2011; Belfer-Cohen and Goring-Morris, 2011). Unfortunately, in spite of the use of floatation techniques in many Natufian open-air and cave sites only minimal information concerning the use of plants is available due to poor preservation (eg, Weiss et al., 2004; Rosen, 2010).

The Natufian hamlets, with rounded brush huts constructed on stone foundations are considered as sedentary or semisedentary settlements due, among other, to the presence of commensals such as house mice and sparrows (Auffrey et al., 1989). Indications for the growth of social complexity comprise public buildings that herald the later Pre-Pottery Neolithic A (PPNA) “kiva”-type of underground semisubterranean, circular buildings, exposed in two sites in the Jordan Valley (Valla, 1988; Grosman et al., 2016).

Natufian sites vary in size with the largest attaining 0.2 ha and contain rich material culture of stone artifacts, bone tools, and ground-stone objects such as mortars, pestles, and art objects. Evidence for the use of bows and arrows is supported by edge damage on the common microlithic lunates (Yaroshevich et al., 2010). The Natufian contexts contained several animal figurines shaped from bone and limestone, and rare human images, as well as a large series of incised slabs displaying various patterns (eg, Belfer-Cohen and Bar-Yosef, 2010). Many of the dead were buried on-site, in either supine or flexed positions, with a tendency toward collective burials in the earlier period and an increase of single burials later (Belfer-Cohen, 1995). Some dead were interred with personal ornaments made of Scapophods (tusk shells), bone beads, and pendants, predominantly in the Early Natufian.

Sickles with glossed blades were demonstrated to have been used in harvesting cereals, straw, and reeds for building purposes. In spite of the rarity of archaeobotanical remains and no evidence for storage, the current

assumption is that the Natufian subsistence relied heavily on the procurement of plant resources as well as hunting and fishing. One may hypothesize that growth of predomesticated cereals was practiced by the Natufians (as assumed for the earlier Ohalo II and in the following PPNA period). Their vegetal diet included wild cereals, pulses, other seeds, and various fruits (Hillman, 2000; Tanno et al., 2013). Meat was obtained by hunting in the immediate environment. The main prey were gazelle, equids, aurochs, some fallow deer, wild boar, wild goat, and small game such as fox, hare, tortoise, and numerous birds (eg, Bar-Oz, 2004; Munro, 2004; Gourichon and Helmar, 2008).

The YD had a major impact on the final Natufian society in the Southern Levant. This period was dominated by variable seasonality, and lower temperatures thus limiting the biome production (Orland et al., 2012; Caracuta et al., 2015; Hartman et al., 2016). Many sites were abandoned but others along the Jordan Valley had survived (Grosman et al., 2016). The Final Natufian groups, who adopted a more mobile settlement pattern, and increased their consumption of low-ranked resources such as juvenile gazelles, bone grease, and fast-moving small game like hare, and slow-moving tortoises (Munro, 2004).

During the end of the YD and the first millennium of the Holocene (c. 11,700−10,300 cal BP) the socioeconomic map of the Levant changed dramatically reflecting the emergence of two related economies (Fig. 19.3). Villages of sedentary foragers spread along the foothills of the Taurus-Zagros mountains along the Tigris River Valley and its tributaries. Farming societies were established in the Euphrates River, its tributaries and further west and south in the Jordan Valley (Bar-Yosef, 2014; Özdoğan et al., 2011).

Among the settlements of hunter-gatherers along the Tigris River and its tributaries, two examples are mentioned here. Hallan Çemi, on the bank of Batman River and that of Körtik Tepe in the Tigris River Valley, with rounded pithouses and built stone walls, distinguished by the production of numerous decorated soapstone vessels (Rosenberg and Redding, 2000; Arbuckle et al., 2014; Benz et al., 2015). Both sites produced a wealth of evidence for the consumption of wild sheep and goat, red deer, wild cattle, and pigs, and the exploitation of various small-seeded plants (Willcox and Savard, 2011). Wild cereals were not available in that area during the YD, and reached it only toward the end of the first millennium of the Holocene.

Farming communities in the Euphrates basin and the Southern Levant archaeologists identified in the earlier phase of the Neolithic, the PPNA (c. 11,700−10,500 cal BP), three cultural entities known as the Khiamian, the Mureybetian, and the Sultanian (Figs. 19.2 and 19.3; Fig. 5.1; Simmons, 2007). PPNA Villages vary in size and reach up to 3 ha, indicating a rapid increase of population, a major energy expenditure invested in buildings (stone foundations, brick walls, and flat roofs), storage facilities (private and public), long-distance procurement of Anatolian obsidian, and the construction of central ceremonial centers (eg, Kuijt, 2009; Schmidt, 2005, 2011; Belfer-Cohen and Goring-Morris, 2011; Goring-Morris and Belfer-Cohen, 2011; Bar-Yosef, 2014). In the Euphrates Valley villages such as Jerf el-Ahmar practiced an economy mostly based on cereal cultivation as detailed later in this chapter, although the increase in the frequency of the domesticated forms occurred later, at the time of the Early Pre-Pottery Neolithic B (PPNB, c. 105,000−82,000 cal BP).

In addition, communication by rivers' transport, described earlier, allowed information to reach Southern Mesopotamia. Claims based on the archaeobotanical assemblages from Chogha Golan for independent initiation of wild barley and wild emmer wheat cultivation (Riehl et al., 2011, 2013) can be refuted. The reported cultivation could be the outcome of information brought in by humans from the "core area" while boating along the Tigris.

The Levantine archaeoobotanical assemblages dated to the PPNA and Early PPNB would fall under the category of predomestication cultivation (Colledge, 2002; Willcox, 2005; Weiss et al., 2006) as observed in the PPNA Netiv Hagdud and Gilgal sites (Weiss et al., 2006). There is no reason to reject the proposal of continued cultivation of the wild species of wheat and barley during the PPNA. Most authorities agree that by 10,500−10,000 cal BP a suite of plants were already partially domesticated and the frequencies of wild forms gradually diminished in the fields as documented during the course of the PPNB period.

Here I follow Willcox's meticulous studies in describing the cultivation and harvesting activities based on the archaeobotanical remains collected in three methodically excavated villages, namely, Jerf el-Ahmar, Tell 'Abr 3, and Dja'ade, on the banks of the Euphrates River (Willcox, 2012; Willcox and Stordeur, 2012). Willcox contends that (1) the assemblages of the recovered plant remains are quantitatively dominated by the founder crops: barley, emmer, einkorn, lentil, and pea, while gathered small-seeded grains decreased; (2) the introduction of founder crops began with barley to which single-grain einkorn and emmer was added. Pulses were introduced a bit later as recorded in Dja'ade, an Early PPNB site, including broad beans (*Vicia faba*) and chickpeas (*Cicer arietinum*); (3) the number and varieties of weed taxa increased, several of which characterize the tilled land prepared for sowing the cereals; (4) grain size of the founder crops in these sites increased and is considered as evidence for cultivation; and (5) cultivation as an annual activity resulted in the loss of seed dormancy among cereals and legumes.

The process for the completion of the domestication syndrome is reflected in the numerous genetics studies and

carbonized assemblages (eg, Peleg, 2011; Willcox, 2012; Willcox and Stordeur, 2012). The conclusion of the various investigations resembles the statement by Peleg et al. (2011) concerning the cross between durum wheat and its wild emmer progenitor, "the number of genes and mutations required for a critical domestication transition has been addressed in many studies. It has been suggested that in many cases, a single gene played a pivotal role in moving the population over the trajectory of a key domestication transition" (Peleg, 2011, p. 5059). However, the length of time for the completion of the domestication syndrome is highly debated.

One view suggests that the time range, well-dated by several hundred radiocarbon dates, lasted from the end of the Late Natufian through the Middle PPNB (c. 11,700–9200/8800 cal BP) and labeled as a "protracted process" (Fuller, 2007; Fuller et al., 2010; Purugganan and Fuller, 2011). In addition, the long process witnessed unsuccessful trials with wild oat, rambling vetch, rye, and wild black lentil (eg, Weiss et al., 2006; Abbo et al., 2013).

A different opinion concerning the length of time it took for the domestication syndrome to establish its genetic changes among the founder crops in the Levant (eg, nonshattering rachis, no dormancy of seeds, etc.) suggests just a couple of centuries (Hillman and Davies, 1990, p. 73). Recently it has been argued that humans were smart and could differentiate between shattering and no-shattering ears and therefore conducted a scheduled selection of tough-rachised ears while harvesting every summer (Abbo et al., 2008, 2010, 2011, 2012, 2013). Moreover, the assumption is that early cultivators knew that the choice of nonshattering ears is advantageous over what is generally available in the wild stands and that they should take this into account in their food preparation techniques. However, if the same food preparation techniques such as the grinding of wild barley witnessed at Ohalo II (Piperno et al., 2004) was employed at a later time, it means that the strategy that every summer a selection of nonshattering ears had to be done, was not practiced in a very long time. If most of the fields were harvested before full maturation, the differentiation between fully domesticated and still wild plants was not an easy task (eg, Snir et al., 2015). Preparation of the wild cereals for making the desired dish was feasible as shown by experimental harvesting and milling (Eitam et al., 2015). It seems that without further information derived from the carbonized plant assemblages, as well as the different types of grinding stones, it will be difficult to resolve the issue of how and when food preparation techniques changed.

In considering the role of the larger Levantine center, statements that the dominance of the domesticated genotypes in the cultivated plants could have only been achieved outside the natural range of the wild progenitors (Jones and Brown, 2007), have no supporting archaeobotanical evidence (Abbo et al., 2012). The entire domestication process occurred in the Levant, and the ensuing successful subsistence system was distributed to and adapted by neighboring groups.

The fully fledged agro-pastoral economy was in place by 9500/9000 cal BP. The map (Fig. 19.3) shows the distribution of the socioeconomic units of the time just before the temporary collapse caused by the "8200 cal BP cold event" (Weninger et al., 2009). The impact of this environmental change was felt in the Southern Levant more than in the northern areas. It is expressed by a gap in the pollen record of the Dead Sea that indicates reductions of rain over its entire basin (Litt et al., 2012). The fast demographic growth in the Levant allowed during the PPNB the formation of large villages known as "megasites," of 12 ha in size and the complex social structure is evidenced through the complex architecture which incorporates both square and rectangular houses, communal endeavors, storage facilities, and so forth (Simmons, 2007; Bouquet-Appel and Bar-Yosef, 2008 and papers therein).

Assemblages of animal bones reveal that during the Late PPNA, procurement by intensive hunting was complimented by the corralling of goat, sheep, cattle, and pigs that became domesticated toward the onset of the PPNB (Vigne, 2011, 2015; Zeder, 2011, 2012). Keeping livestock required a change of attitude among foragers, and probably by hunters who we assume were the males (eg, Bird, 1999; Waguespack, 2005). This was a more dramatic shift that involved the treatment of plants, which was often a female task. The techniques involved in keeping animals in captivity and intentional breeding was different when the four species are considered. The process of cattle domestication, whether for religious reasons (the "bull-cult"; Cauvin, 2000) or for economic ones, occurred mainly during the PPNA (Vigne, 2011). Similar to other animals, bulls were ceremonially sacrificed, during feasts, as indicated by the faunal assemblage at Göbekli Tepe, a well-known ceremonial center in the northern Levant, on a hilly ridge overlooking the Balikh Valley (Schmidt, 2011). Sacrificing male animals became a common practice in the Levant and Mesopotamia in later millennia (Albright, 1957). Cows were often spared, especially during late Neolithic times when milk consumption became a daily habit, while bulls were either sacrificed or kept in very small numbers. These reversed ratios between bulls and cows are exemplified when comparing the female–male ratio in Göbekli Tepe, as a place for rituals and in the nearby PPNB village of Gürcütepe where most of the slaughtered cattle were cows (Peters et al., 1999).

The process of adopting goat and sheep husbandry in the Northern Levant evolved during the PPNA and later in the course of the PPNB resulting, together with plant cultivation, in the full appearance of agro-pastoral societies (Vigne, 2011; Zeder, 2011). Considering the intracenter

relationships we should note that it took between 500 and 1000 years for goat and sheep to spread into the Southern Levant (Martin and Edwards, 2013). The herding of these animals could have been a part of the long-distance exchange of obsidian from central Anatolia or marine shells from the Red Sea of some 1000−1500 km afar, such as the shells found in Abu Hureyra (Ridout-Sharpe, 2015).

Pigs became a component of the agricultural package in the core area of the Northern Levant after goat and sheep, at the same time as the cattle (Vigne, 2011). The best records for their domestication in the Northern Levant and the dispersal through the Southern Levant are derived from the Late PPNA and become more numerous in Middle PPNB sites (9000−85,000 cal BP; Horwitz et al., 1999). They reach the lowlands in the southern end of the Zagros by 6000 cal BP.

Local transmission in the Levant did not cease as shown by the delayed adoption of chickpeas, faba bean, and fenugreek. The first two were brought into the Southern Levant a few 100 years later (Tanno and Willcox, 2006; Caracuta et al., 2015), while the fenugreek (*Trigonella* sp.) is recorded for the first time in Tell Halaf at c. 6000 cal BP (Zohary et al., 2012).

At the same time, in general, farmers expanded into Anatolia. Sites such as Asikli Höyük (at c. 10,200), and Çatalhöyük (at c. 9100 cal BP) were founded on Levantine farming economy including domesticated goat, sheep, cattle, and pig (Arbuckle et al., 2014). The dispersion of the farming package continued to expand and reached the Bosphorus straights by c. 9500 cal BP and then farmers began to migrate into Greece and the Balkans (eg, Özdoğan, 2011).

The eastern portion of the Fertile Crescent is not less important. The geographic continuity of the Taurus−Zagros arc, their intermountain valleys as well as their foothills along the Mesopotamian plain, saw the rapid expansion of farming communities. The Tigris and the Euphrates rivers assisted in the fast spread of domesticated plants and animals, and among the better known early farming communities are those situated in the Deh Luran plain (Hole, 1987).

An important aspect for this review is the food preparation techniques. In Southwestern Asia, the kitchen was based on making bread. Cereal grains were stored in baskets, silos, and underground pits and by mid Holocene were replaced by large ceramic containers. With bread as a basic element there was no need for pots that began to appear at about 9000 cal BP and increased in infrequency during the eighth and seventh millennia BP when the production of liquid food such as beer, wine, milk, and oil started. The basics of the Southwestern Asian kitchen spread with the founder crops to other geographic regions. It is a markedly different trajectory compared to that from East Asia where steaming was probably the reason for the emergence of pottery during the Late Pleistocene (see later in this chapter; Fuller and Rowlands, 2011) (Fig. 19.4).

During the Middle Holocene fruit trees became an integral part of the agricultural package as they were probably in earlier times in the tropical belt of Meso-Central America and Northern South America. Trees present a difficult task for archaeobotanists because, unlike the change in the morphology or the disarticulation in domesticated cereals, fruit stones, pips, pollen, or nutlets rarely demonstrate diagnostic or morphological traits that separate the wild from the domesticated varieties (Weiss, 2015).

Southwestern Asia contributed also to the domestication of several trees. The first was the fig tree (*Ficus carica*) since the Early Holocene (c. 11,700−10,500 cal BP) in the Jordan Valley, later found in many other localities (Kislev and Hartman, 2012). Olive trees were second, domesticated in the Northern Levant around 7800 cal BP (Weiss, 2015). Olive oil was identified in pottery dated to c. 6800 cal BP, in the Early Chalcolithc period (Namdar et al., 2014). Wild grapevine (*Vitis silvestris*) is recorded archaeobotanically in archaeological contexts since c. 8200−6150 cal BP and is known from Western and Northern Europe as well as the Caucasus region. However, the evidence for the domesticated species (*Vitis vinifera*), which is self-pollinated, dates only from some 5500 years ago. Tartaric acid that is considered as the residue of wine was traced in pottery in Iran and the Caucasus from contexts dated to the eighth millennium cal BP and later (McGovern, 2003). The date palm (*Phoenix dactylifera*), a semiarid tree, was domesticated during the seventh millennium cal BP in Egypt and Mesopotamia. In sum, except for the fig, all other fruit trees and their products appear since 8000 cal BP, in the second part of the Holocene.

In sum, the archaeological data obtained in the Levant was employed by different scholars to present hypotheses that should explain why people began to cultivate (eg, Bellwood, 2005). One approach sees the change in the spatial arrangements of social units, motivated by climatic fluctuations and competition to start cultivating in an environment rich in resources. The opposing view suggests that this richness attracted the desire for creating surplus that could be used for social gains I will return to this issue in the final discussion. However, there is no doubt that the change from rounded houses to rectangular ones reflect changes in the social structure with the full fledge farming (Flannery, 1969, 2002).

China

Two East Asian centers for the emergence of agriculture are known from China. A North China center is characterized by dry farming based on the growing of broomcorn (*Panicum miliaceum*) and foxtail (*Setaria italica*) millets and soybean. The second center, in South China, was

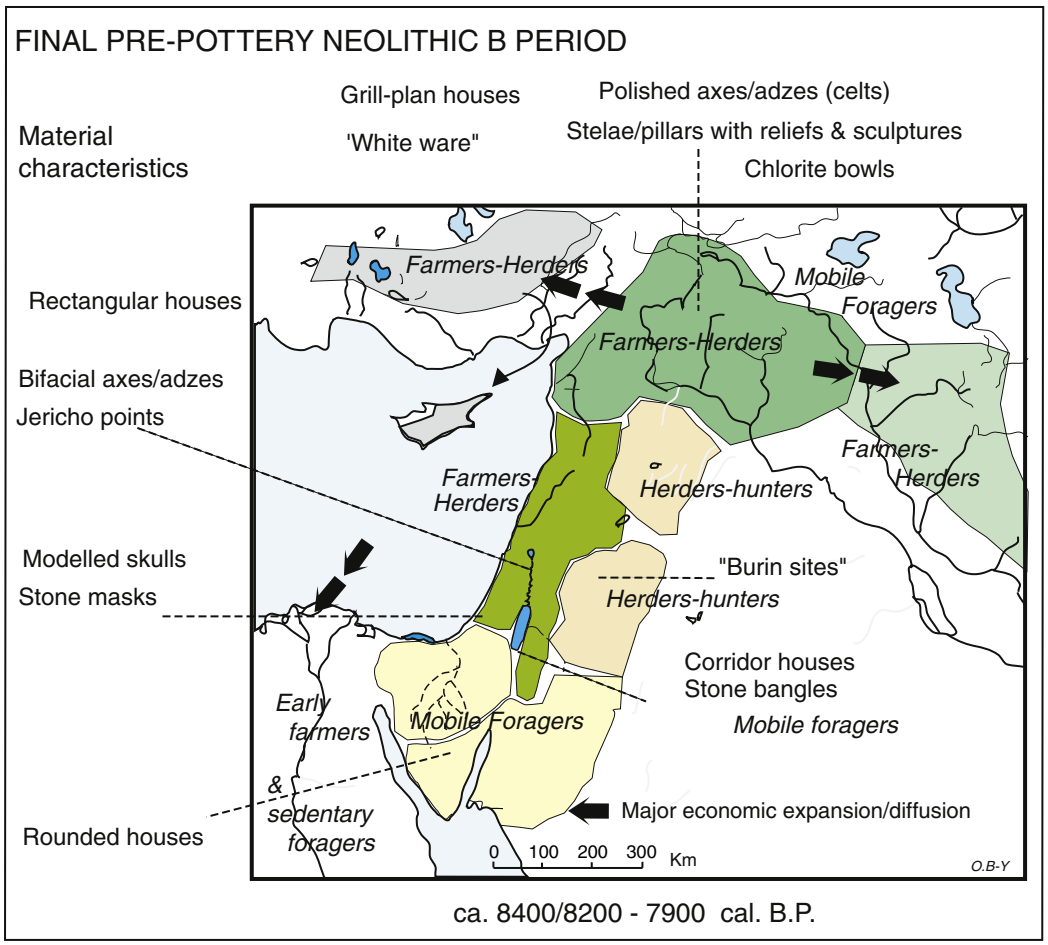

FIGURE 19.4 A map of socioeconomic entities at the time when the Neolithic Revolution was completed and before the temporary collapse caused by a short-term dry and cold event around 8200 cal BP.

characterized by rice cultivation with the development of paddy fields. Archaeobotanical remains include assemblages obtained by flotation and of starch grains retrieved from grinding stones and other stone objects. The gathered information, which is rather sparse given the size of this country, indicates that before agriculture, the two millet species were collected by hunter-gatherers and consumed like other plant foods (eg, acorns) during a long period, c. 25,000−11,500 cal BP (Liu, 2015; Liu et al., 2013; Yang et al., 2015). Starch grains and seeds of wild foxtail millet and *Echinochloa* sp. were uncovered in Shizitan 9, dated to 13,800 to 11,600 cal BP; this locality is an ephemeral site of foragers situated on the banks of a tributary of the Yellow River (Liu et al., 2011; Bestel et al., 2014). Similar information was obtained during the excavations of sites located in the eastern lowland plains that border the Taihang and Yan mountain chains (Fig. 19.5). In three sites here, Donghulin, Zhuanian, and Nanzuangtou, dated to c. 11,000−9500 cal BP, there was evidence for the use of millet (Bettinger et al., 2007; Cohen, 2011; Liu et al., 2010; Zhao, 2010, 2011; Yang, 2012). In Donghulin, the remains of a semisubterranean rounded house were uncovered including a couple of burials and a wealth of material culture comprising grinding stones, hafted bone handles, microblades, pottery, and more, indicating the presence of a semisedentary hamlet. Hunting and gathering formed the subsistence base. None of the available information indicates as yet intentional growth of millet or other plants, although most of the archaeobotanical evidence (gained through starch analysis) from the three sites is indicative of foragers practicing a certain level of cultivation (Zhao, 2011; Liu, 2015; Yang et al., 2015a).

Archaeobotanical information indicate the wide distribution in Northern China of dry land farming of millets, but the original center of domestication is yet unknown. Genetic studies documenting the presence of broomcorn millet in Eastern European assemblages at c. 7000 cal BP (Hunt et al., 2011) raise the question whether the millet domestication occurred in a single or multiple centers, with the option for an additional center in Central Asia. The resolution of this issue will depend on new archaeobotanical material. The area in China that seems most suitable for

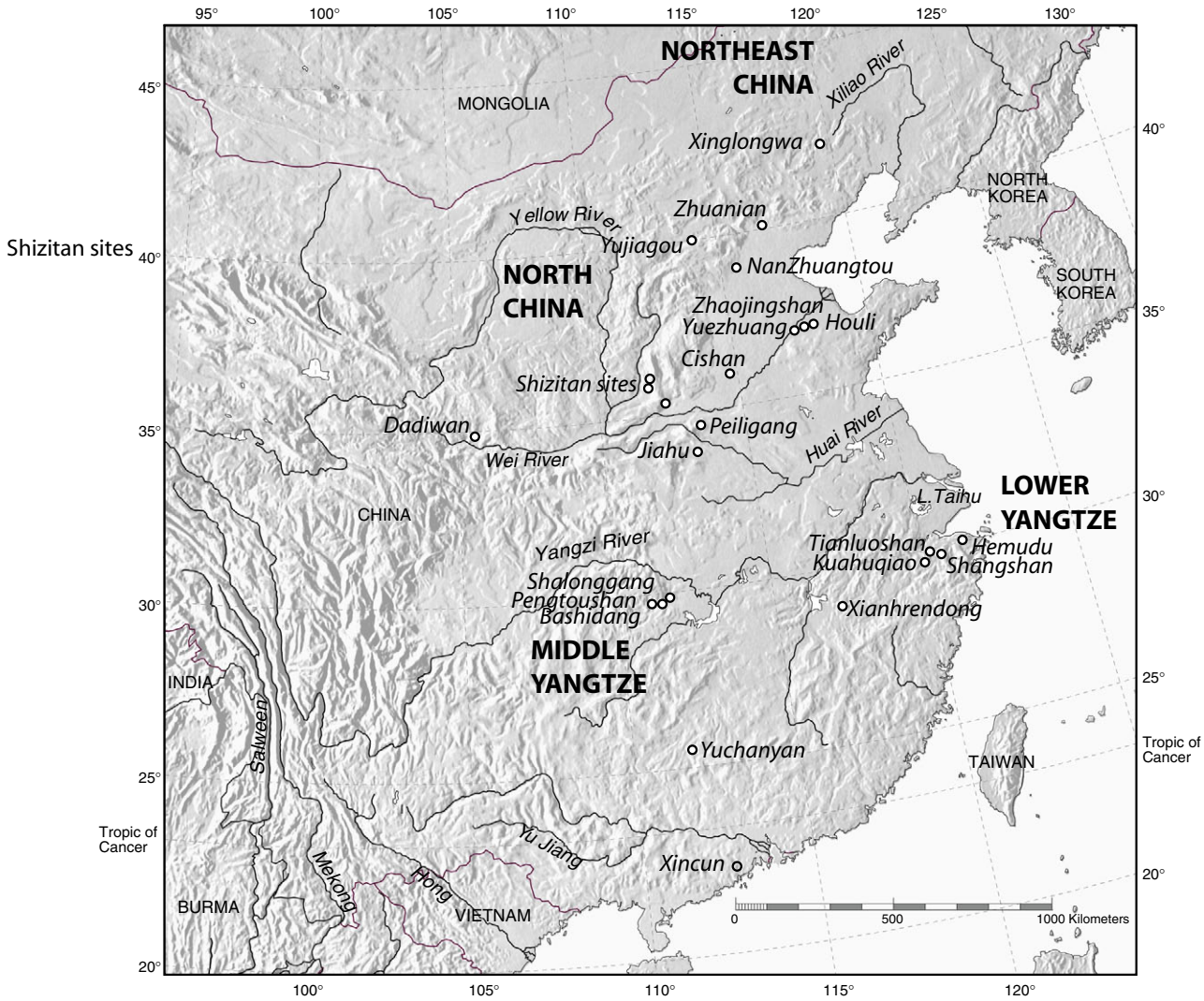

FIGURE 19.5 Late hunter-gatherers and Early Neolithic sites in China. Several sites are mentioned in the text and others can be found in the cited sources. *Modified from Cohen, D.J., 2011. The beginnings of agriculture in China: a multiregional view. Current Anthropology 52, S273–S293.*

millet domestication is the lower Yellow River basin (Lu, 1999; Shelach, 2000; Bar-Yosef, 2011; Cohen, 2011).

The earliest evidence for domesticated broomcorn and foxtail millet in Northern China was uncovered at Xinglongwa (c. 8000–7500 cal BP), a site situated near the Liao River along the Mongolian grasslands (Lee et al., 2007; Zhao, 2011). This village comprises a cluster of over 50 rectangular houses with a central, larger house of the local chief (Liu, 2007). The material components include pottery, stone and bone tools, and the earliest-known jade objects. The consumption of millet species—a C4 plant—was traced by stable isotopes in human bones (Barton et al., 2007, 2009), although their domesticated status is not clear. Direct evidence for an economy based on growing what are definitely domesticated species of millet as well as pigs is documented in Neolithic sites closer to the Yellow River; by c. 8500–7500 cal BP, these sites of the Peiligang-related cultures spread also into the Huai River basin (Fig. 19.4; Zhang and Hung, 2012; 2013). Among the famous Yellow River sites is Cishan, a ceremonial locality dating c. 7500 cal BP with impressive evidence for the scale of millet use, including 5 m deep storage pits containing the remains of millet grains (Zhang and Hung, 2013). Unfortunately, a previously reported date for Cishan of c. 10,000 cal BP (Lu et al., 2009) was erroneous, but is still being repeated in numerous publications.

Assuming that millet cultivation evolved within a core area in the large basin of the Yellow River, dispersals in different directions would be expected; these are seen northward to Xinglongwa and westward through river transport to Dadiwan (Fig. 19.4; Cohen, 2011). An overlapping of the two economies of millet and rice took place in the area of the Huai River that lies between the Yellow and the Yangtze rivers.

South of the Yellow River in the Huai River basin, excavations at Jiahu exposed a village of 50 ha in size with rounded houses in its lower layer dated to c. 8500 cal BP, and square houses in the upper two layers. The rich finds include the well-known bone flutes, bone arrowheads, and elaborate pottery assemblages (Zhang and Hung, 2013). Fully domesticated pigs were identified both morphologically and genetically (Cucchi et al., 2011; Zhao, 2011). Jiahu was also one of the first sites where flotation was carried out, and the retrieved collection included a wealth of charred plant remains, with such edible plants as tubers (eg, lotus roots), acorns, water caltrop, chestnuts, rice, wild soybean, and more (Zhao, 2010, 2011). The weedy grasses included several taxa such as *Digitaria* sp. and *Echinochloa* sp. that may have grown in rice fields. Early rice remains were also reported from Baligang, some 300 km southwest, on the bank of the Han River that flows south as a tributary of the Yangtze River (Deng et al., 2015). A question for future research is whether soybean domestication occurred in China or Korea (Lee et al., 2011): the presence of soybean at Baligang dating to after 7000 cal BP (Deng et al., 2015) does not resolve this issue.

The occurrence of rice at Jiahu c. 8500 cal BP raises another issue concerning where and when rice was domesticated. For several decades, the Pengtoushan-Bashidang culture area in the middle part of the Yangtze River basin was seen as the "core area." Another option was added with excavations in the lower Yangtze valley of several waterlogged sites (eg, Shangshan and Hemudu-related sites) that produced domesticated rice remains dating about 8000/7800 cal BP. Currently, the late foragers who could have been the ancestors of the local farmers who first domesticated rice are better documented from the lower Yangtze. Here, the sequence at Shangshan, a sedentary village, began with the cultivation of barnyard grass (*Echinochloa* sp.) at c. 11,000−9000 cal BP, based on starch and phytoliths analyses retrieved from grinding stones and other objects (Yang et al., 2015). In addition, other grasses of the Triticeae family and wild rice are present. Only the later phase of Shangshan corresponds culturally to Kuahuqiao, another Neolithic village located in the same area, where the appearance of a mixed assemblage of wild and domesticated rice is dated to c. 8000/7800−7400 cal BP (Zheng et al., 2007). Rice assemblages at Tianluoshan, a neighboring site that dates to c. 6900−6400 cal BP demonstrates an increase of domesticated rice in its assemblages (Fuller et al., 2009). In all these sites, water chestnuts (*Trapa*), acorns, and other gathered plant species are still a major part of the local diet, in addition to fishing and hunting deer and wild pigs. Experimental studies indicate that boiling rice grains prior to grinding reduces the chance of their starches being preserved on the flat surfaces of milling slabs. The deep roots of steaming as a common procedure for food preparation are likely indicated by the production of pottery in South China since 20/19,000 years ago (Wu et al., 2012; Fuller and Rowlands, 2011).

Without delving into the issue of whether rice was first domesticated in the lower or the middle part of the Yangtze basin, the sequence in the former area clearly indicates that sedentary hunter-gatherers were involved in cultivation (Lu, 1998). In addition, the dispersal of rice cultivation is evidenced by rice phytolith remains from several sites, such as Dingsishan and Xiaojing, both in Guangxi Province, located some 500 km south of the Pengtoushan area, and dating to after c. 6000 cal BP (Zhao, 2011). Indeed, the rate of dispersal from the center of domestication into the vast region of Southern China resembles the rates within the terrestrial environment of the Levant (see earlier).

Further from these potential centers, current evidence for plant exploitation in subtropical Southern China comes from Xincun, a coastal village dated to c. 5000 cal BP. Starch and phytolith analyses indicate a subsistence strategy based on gathering a wide range of edible plants, such as sago palm, banana, water chestnut, lotus root, arrowhead, ferns, Job's tears, and acorns (Yang et al., 2013). Rice traces were identified as well, but their role within the local economy is not clear.

Here, genetic studies of the origins of domesticated rice should be briefly mentioned, as well. The authors of one review clearly state that "Lately … genetics has told us a constantly changing story" (Gross and Zhao, 2014, p. 6193). The best available genetic scenario for the history of domestication is that of the wild rice, *Oryza rufipogon*, which was distributed over vast landscapes in China and other regions of East Asia including varieties found in the Ganges River Valley in India, was domesticated by more than one human population. There is a tendency in most genetic studies to view the original domestication as occurring in the Yangtze River valley, due to the appearance of *Oryza japonica* remains. Recognizing the well-accepted introgression between the cultivars *japonica* and *indica*, Gross and Zhao (2014, p. 6196) offer two possible interpretations: either *Oryza indica* was the result of an independent local domestication or there was only a single domestication event—of *japonica*—"with *indica* [then] being brought to a domesticated state through a series of hybridization events between *japonica* and *O. rufipogon* populations" (Gross and Zhao, 2014, p. 6196).

THE SPREAD OF AGRICULTURE TO THE "NONCENTERS" AND ITS IMPACTS

Europe and the Mediterranean Basin

Close to the Levant and Anatolia is Cyprus. Early navigation of a minimal distance of 35 km of open water by Terminal Pleistocene foragers brought the wild pig to the island (Vigne et al., 2012). The size and dates of bones uncovered in the Arcrotiri-Aetokremnos rock-shelter

indicate that the wild suids were brought over at c. 11,700−11,400 cal BP. Later, the lack of predators caused their size to decrease, as expected for island populations, and evidenced when their descendants were hunted by the first settlers who built rounded houses in Klimonas some 10,600 years ago (Vigne et al., 2012). By 10,400 cal BP the Levantine farmers brought from the mainland the full agricultural package of cereals, legumes, goat, sheep, cattle, and pigs, as well as fallow deer, dogs, and later, the cat (Vigne and Cucchi, 2005; Vigne, 2013, 2015).

The expansion of Southwestern Asian farmers from Anatolia into Europe was known for many years, documented by archaeobotanical and archaeozoological studies of numerous assemblages, as well as paleogenetics (Fig. reviews in Zohary et al., 2012; Bellwood, 2005; Diamond, 1997). The first study of human movements across Europe, suggested by A. Ammerman and L. Cavalli-Sforza (1984), was labeled the "wave of advance." This demic-diffusion by people carrying the agricultural package caused partial replacement of the local Late Paleolithic hunter-gatherers (Cavalli-Sforza and Feldman, 2003). Corroborating evidence for the transmission of crops through exchange and during the actual spread of farming population was shown, for example, by barley's phylogeography across Eurasia (eg, Jones et al., 2012). Migrants and transmissions occurred along the Danube River and further west by the Rhine River and their tributaries. The other path was coastal navigations across the Mediterranean Sea, first along the northern coast and later along the African coast. Farmers first colonized the Mediterranean islands and then the coastal areas of Italy, France, and Iberia (eg, Zilhao, 2014). Later they moved inland, took over large areas from the endemic Mesolithic foragers, and interbred with them in several areas. Recent paleogenetic studies document additional human dispersals from the Asian steppe into Europe during the second half of the Holocene (eg, Haak et al., 2015; Jones et al., 2015; Pinhasi et al., 2012; Veeramah and Novembre, 2014).

Controversies over whether the agricultural package could have been partially the result of local domestications by Mesolithic foragers were resolved by detailed studies of goat, sheep, pig, and cattle that demonstrated their Asian origins (eg, Rowley-Conwy, 2011). The same statement relates to the domesticated plants. Proposals that elements of the same package were adopted by local Mesolithic foragers, coexisting during a few centuries to over 2000 years with the incoming farmers, were based on scanty evidence. Debates concerning the possible domestication of the European aurochs that survived until the 17th century AD were recently resolved. The combination of archaeozoological and genetic analyses demonstrated that local aurochs did not contribute, or only to a very limited extent, to the domestic cattle in Europe whose origins are traced to Southwestern Asia (Tresset et al., 2009).

One of the major farming cultures is the Linear Band Keramik (LBK) that originated in the Carpathian basin and moved across central Europe, while in the Mediterranean Europe the later Cardial pottery designates another set of farming groups. The LBK farmers moved from one loess area to another, often along river valleys. There are other cultures identified by their typical pottery types. The detailed evidence (eg, Rowley-Conwy, 2011 and references therein) indicates, as already suggested in the past (van Andel and Runnels, 1995), that the monolithic wave of advance was constructed of sporadic and punctuated movements of farmers. Constant interactions between the incoming farmers and local Mesolithic foragers probably contributed to some degree of population mixing. However, the basics of the southwestern Asian agro-pastoral package were adopted across Europe except for the northern belt where reindeer pastoralism evolved during the later Holocene.

Korea and Japan

Since Paleolithic times the Korean peninsula was on the receiving end of cultural changes and human migrations from the vast terrestrial region of East Asia. Its geographic situation can be compared to the position of Europe on the western end of Eurasia. With the development of seafaring additional arrivals could have taken place, and the narrow straights that separate the Japanese archipelago from the peninsula did not limit crossings at different times. The current political situation hampered the efforts to connect the research between Northeast China and South Korea but the intensive investigations in the latter allows us to describe plant cultivation by sedentary village inhabitants that preceded the arrival of millet cultivation (Lee, 2011).

Similarly to other regions where the information is available for Early Holocene cultures, the evidence in Korea comes from the Chulmun culture, subdivided into Early (c. 7500−5500 cal BP), Middle (5500−4000 cal BP), and Late (4000−3400 cal BP) phases. During the Early Chulmun, vegetal economy continued the broad spectrum of previous generations with some presence of millet in the context of rounded dwellings. While being village inhabitants they were hunter-gatherers and fishers as the culture is known from the early excavations spread along the coast and river banks where they formed numerous middens. Their exploitation of marine resources was accompanied by a low level of plant cultivation and storage. The number of villages characterized by plant cultivation increased during the Middle Chulmun due to the introduction of broomcorn and foxtail millet.

A short distance across the Korea Straights is the southern part of the Japanese archipelago, where the earliest Paleolithic sites are dated to c. 40,000 cal BP. The preceding upper Paleolithic contexts were rich in stone tools, and other hard rock objects (such as axes) were

uncovered. Microblade industries originating in continental East Asia are documented in Hokkaido at c. 22,000 cal BP and in Kyushu at c. 16,000 cal BP. At about this time, pottery made its appearance on the islands.

The Paleolithic sequence was followed by the onset of the Jomon culture subdivided into a few phases. The Incipient Jomon coincides with the onset of pottery making (c. 16,400−11,200 cal BP). The subsequent Initial phase lasted from c. 11,200−7250 cal BP, and the Early Jomon from c. 7250−5540 cal BP. The basic subsistence was similar to that of the Paleolithic period with continued hunting, fishing, and gathering by semisedentary and sedentary communities. During the earlier times oaks were used for building houses but during the course of the Middle Jomon (c. 5500−4500 cal BP) were replaced by chestnut trees (*Castanea crenata*). The recovered evidence in Eastern Japan sites shows the correlation between the dominance of arboreal pollen in the cores and the charcoal assemblages in the excavations. The shift to the durable, easier felling of chestnut trees, with stone axes that were in the tool-kits of the foragers in the islands since the Early Upper Paleolithic, is interpreted as "agricultural" activity. In addition, from the Early Jomon the lacquer trees (*Toxicodendron vernicifluum* and *Rhus javanica*) were either introduced at that time from China or were naturally grown in Japan, Korea, and China (eg, Crawford, 2011; Noshiro and Sasaki, 2014).

Direct evidence for cultivation of annual plants is that of the barnyard (*Echinoloa crus galli*), the ancestor of the Japanese millet, identified in the excavations of Nakano B, a village site with squarish pit-houses in Southwestern Hokkaido dated to 9000−8700 cal BP (ie, Initial Jomon period). The discovery "strongly suggests that it was going under selection akin to domestication" (Crawford, 2008, 2011, p. 448). This activity occurred in the context of systematic collection of small grains and leafy green plants including bottle gourd, hemp, and others as well as fleshy wild fruits including nuts which lasted from the Initial through the Middle Jomon periods. In addition, the economic strategy of the Jomon people included fishing and hunting. Not surprisingly the argument whether to refer to these societies as "affluent foragers" or by some other term (Crawford, 2008 and references therein) makes no difference if the direct evidence demonstrates that the original population of the Ainu practiced "plant husbandry" or "marginal cultivation" and made pottery, similarly to the Chinese villagers in the lower Yangtze River basin (Yang et al., 2015). The important issue is identifying the nature of the socioeconomic trajectory of those communities. In the case of the Japanese archipelago the major revolutionary change occurred with the invasion of the rice-growing farmers from Korea some 2800 years ago bearing the Yayoi material culture who, through the process of taking over most of the archipelago, became the recent Japanese.

Southeast Asia and India

The information concerning rice domestication in the Yangtze river basin can be tied with the dispersal of rice farming that reached coastal China by about 5000 cal BP and dispersed directly by farmers and indirectly through products into Southeast Asia slightly after 4500 cal BP (Bellwood, 2005; Higham, 2015). The origins of migrants and products were in the southern vegetation belt of China where charred remains of roots and tubers were recovered in the Zengpiyan cave (Zhao, 2011). This tropical and subtropical belt was according to C. Sauer the origins of all agricultural systems (Sauer, 1952). He suggested that vegetative propagation should logically precede grain-based cultivation. Edible roots and tubers that reproduced asexually are easier to handle than self- or wind-pollinated plants.

Undoubtedly, the cases of Borneo, Philippines, the Indonesian islands, and New Guinea could support Sauer's model but the archaeological evidence is yet insufficient. In the islands and archipelagos such as the Philippines the introduction of rice as staple food was brought by Neolithic migrants some 4000 years ago and adopted by local hunter-gatherers who domesticated the banana, sugar cane, taro, and yam (eg, Barker and Janowski, 2011 and papers therein; Denham, 2011; Bellwood, 2013).

In New Guinea the history is divided to the periods before and after the arrival of the Austronesian Neolithic migrants around 3500 cal BP. Studies of indigenous domesticates of fruits and tubers included in the highlands the *karuka* Pandanus complex (*Pandanus julianettii/iwen/brosimos* complex), edible *pitpit* (*Setaria palmifolia*), and Rungia (*Rungia klossii*), and in the lowlands the species of *marita* Pandanus (*Pandanus conoideus*), *Canarium* spp., and *Terminalia* spp., as well as sago (*Metroxylon sagu*). Several species have broad altitudinal range such as sugarcane (*Saccharum officinarum*) and the Australimusa bananas (*Musa* spp.) while the original environment of the tuber *Pueraria lobata* is unknown. Archaeologically it was demonstrated that employing the vegetative propagation occurred together with the development of cultivation on mounded fields or "swamp gardens" around 7000−6500 cal BP while ditched fields, draining the extra water appeared by c. 4,000 cal BP, led to increasing degrees of domestication (Denham, 2011; Fullagar et al., 2006).

Dispersals westward of rice farming occurred across terrestrial routes or by coastal navigation into India (eg, Fuller, 2011; Fuller et al., 2011; Gross and Zhao, 2014). Recent survey indicates that the earlier agriculture system was established in the Indus due to transmissions from Southwestern Asia of a portion of the agricultural package c. 9000−8500 cal BP (Meadow, 1996). Other agricultural systems attributed to the Neolithic period were those in the Ganges River Valley. Several could have been a result of

relationships with South China. Others were possibly local initiations. The late foraging sites, known as Mesolithic, are dated to a long period from 12/10,000 cal BP through c. 4000 cal BP (Fuller, 2007 and references therein). In most regions of the Indian subcontinent farming is reported as beginning after c. 6000 cal BP with late persistence of foraging societies in the various areas but especially in the southern region (eg, Lukacs, 2002). The paucity of detailed reports from Late Pleistocene and Early Holocene foragers' sites prevents testing the social processes that were responsible for the emergence of cultivation. It leaves the impression that India was a noncenter and that the emergence of local domesticates was due to the introduction of foreign plants (Fuller et al., 2004).

Africa

The African world presents a set of interesting questions concerning the study of the origins of agro-pastoral societies when compared to Asia. Its gross geographic subdivision includes four types of environments: the Mediterranean landscapes in the north and the southern end, the Sahara as a planetary desert, the tropical West and Central Africa, and the savanna lands in the east. The huge area of the continent south of the Sahara did not produce any evidence for early domestication of neither plants nor animals.

The earliest dispersal of farming was into Egypt, the Nile Valley, and along the Mediterranean coastal lands through the Maghreb. Currently the best evidence indicates connections with the Levant, slightly before and mainly after the collapse of the "8200 cal BP cold event," whether by sea or by land through Sinai and the Red Sea coast (Bar-Yosef, 2001; 2013; Weninger et al., 2009; Wengrow et al., 2014). Domesticated crops such as wheat, barley, and broad bean were introduced from their indigenous Levantine homeland, as well as goat and sheep, at about 9000−8000 cal BP (Wetterstrom, 1993, 1998; Holdaway et al., 2016). Movements of humans along the Red Sea, with active communications with people in the Arabian Peninsula are recorded in current genetics (Hodgson et al., 2014). In the western direction the presence of Southwestern Asian founder crops such as einkorn, emmer and naked wheat, naked barley, and broad bean, are recorded by 7200 cal BP in a few Early Neolithic sites in Morocco (Morales et al., 2013; Linstädter et al., 2012; Zilhão, 2014). As somewhat similar dates among Early Neolithic sites characterize the sites on the Iberian coast it is suggested that either both coastal areas were colonized at the same time or that an interaction between the two areas was an ongoing process.

Returning to the southern direction, a question should be raised. Can we observe an impact by migrants from Southwestern Asia in transmitting seeds, animals, techniques, and ideas to Africans who inhabited the Sahara and the Sahel-Savanna belt south of the desert? Genetics, as mentioned earlier, indicate that the strongest impact of long-distance connections of Asians is mostly recognized in Ethiopia and the Horn of Africa (Gallengo Llorente et al., 2015; Hodgson et al., 2014). On the western side of the continent we have no data that could indicate an impact of transmission of information concerning intentional cultivation from the Maghreb where the Southwestern Asian agricultural package arrived earlier then local millet cultivation.

The main and most intriguing controversy concerns the domestication of the cattle (*Bos taurus*) in the Eastern Sahara. Indeed, the number of cattle bones is rather small. The original observations were based on the excavated material in Nabta playa about 100 km east of the Nile Valley (Gautier, 2001) and later during additional excavations in the site of E-06-1, one of the El-Adam clusters of Neolithic sites (Jórdeczka et al., 2013). In this site remains of simple hut floors were exposed including fireplaces, grinding stones, pottery, ostrich eggshell beads, and animal bones. Radiocarbon dates place the deposits at c. 10,300−10,000 cal BP. The authors suggest that the cattle was domesticated or tamed by the bearers of the Arkinian culture in the Nile Valley (Jórdeczka et al., 2013).

An alternative explanation is offered by the genetics investigations demonstrating that taurine cattle was domesticated in Southwest Asia and was introduced to Africa, possibly from Arabia to the Horn region. Later, as expected, the domestic African cattle show genetic contributions from wild African aurochsen males. Finds from the later millennia of the Holocene indicate additional genetic complications due to the impact of the introduction of the Indian cattle (*Bos indicus* or *zebu*) during later millennia (eg, Stock and Gifford, 2013). However, the Sahara was originally the home of Late Pleistocene foragers. With the increasing aridity they continued to survive in oases. Mobile herders with cattle, goat, and sheep, originating in the Nile Valley, expanded through this vast desert region reaching the Western Sahara by some 5000/4000 years ago. The three milk-producing animals were adopted by local populations living on the boundary of the tropical forest, recorded archaeologically at c. 4000 cal BP. It is suggested that the new subsistence strategy did allow for the dietary additive of milk drinking but its main advantage, understood now due to genetic studies, is the decrease of mortality caused by malaria (Cordain et al., 2012).

Here we should note Harlan's remark concerning African environments south of the Sahara that "unlike the Near Eastern African crops lack cohesion. Many have limited distributions; some are found only in some limited areas of West Africa" (Harlan, 1992, p. 182). The main difference between the domesticated species of the two regions is that the African plants have a tendency to be

cross-pollinated. Therefore, in order for domestication to succeed they should be planted away from their natural habitat.

Different domesticated species are recorded in limited areas within the Sahel belt as well as the savanna–forest belt that stretches across the continent (Figs. 19.6 and 19.7). The range of land races include the Pearl millet (*P. glaucum*) that characterizes the drier areas and is found in Mauritania at c. 4000 cal BP (Amblard and Pernés, 1989). In the savanna–forest belt that borders the tropical forest Guinea rice (*Oryza glaberrima*), fonio (*Digitaria exilis* and *Digitaria iburu*), Guinea yam (*Dioscorea retundata*), oil palm (*Elaesis guineensis*), cowpea (*Vigna unguiculata*)—an important legume species and its relative plant, Bambara groundnut (*Voandzeia subterrane* or *Vigna subterranea)*—were exploited and eventually domesticated by the local population (Harlan, 1992; Bellwood, 2013; Asersea et al., 2012; Oas et al., 2015).

Northern Sudan shares the climate of the Sahel belt and South Sudan, especially its southernmost margins, enjoys the climate and vegetation of the marginal Ethiopian highlands. This region produced archaeobotanical assemblages introduced from Egypt, one or 2000 years later, recovered during the excavations of Neolithic villages. The White Nile River was probably the highway that allowed bringing Southwestern Asian domesticates into Sudan. Southern Sudan, affected by the monsoon system, shared the Holocene economy with the north as well as the Ethiopian environments.

The highlands of Ethiopia, on the eastern end of the Sahel, are characterized by topographic heterogeneity, climatic, and soil variability that favors the presence of a large number of land races. In spite of the number of domesticated species it is not seen as a "center" (Harlan, 1992; Fig. 19.7). The plants are sorghum (*S. bicolor*) that expanded westward in the Sahel, finger millet

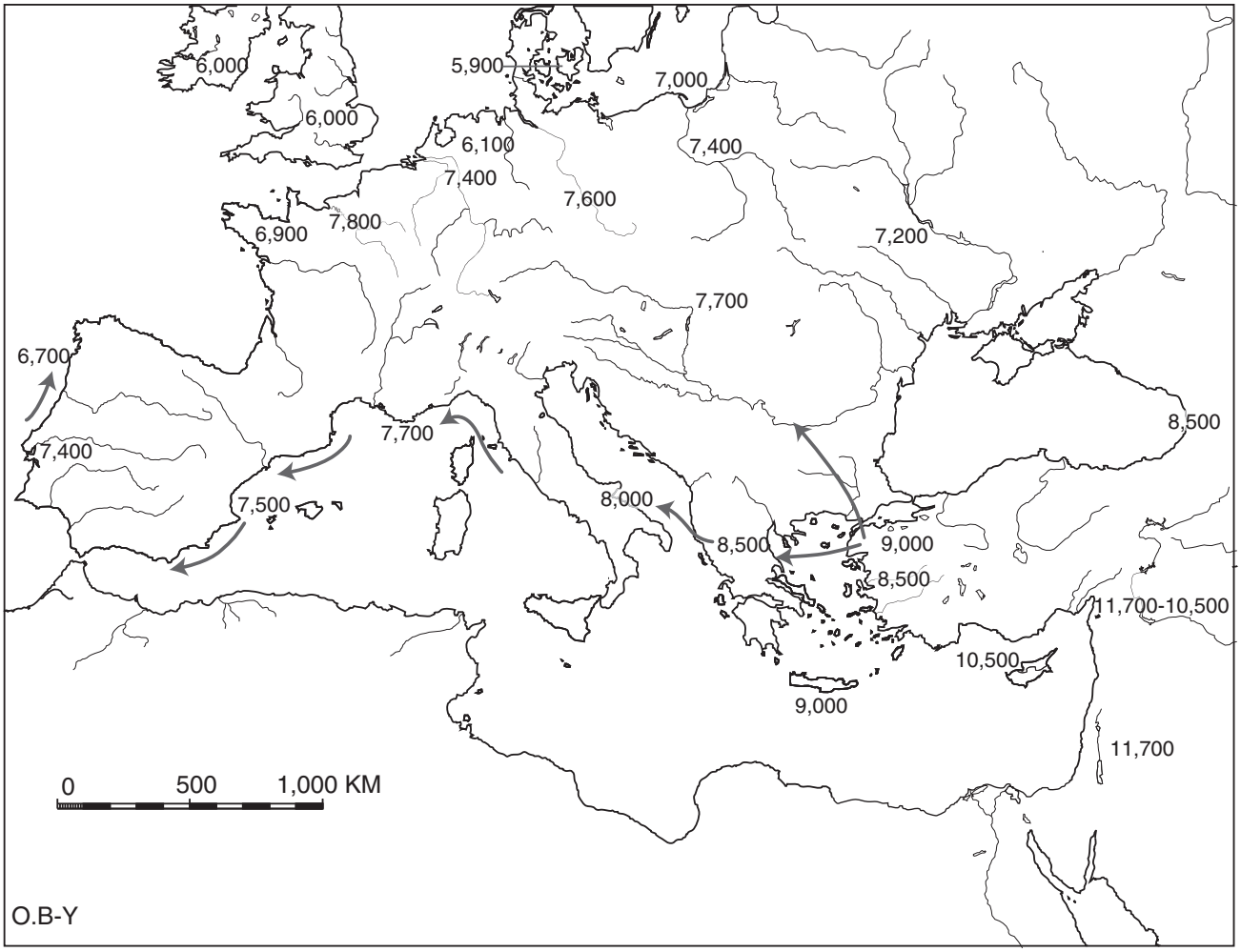

FIGURE 19.6 Dispersals of Neolithic farming groups by and sea and the transmission of the "agricultural package" through terrestrial Europe and along the southern costs with cal BP dates of selected areas. *After Rowley-Conwy, P., 2011. Westward Ho! The spread of agriculturalism from central Europe to the Atlantic. Current Anthropology 52 (S4), 431–451; Bellwood, P., 2013. First Migrants: Ancient Migrations in Global Perspective. Wiley Blackwell.*

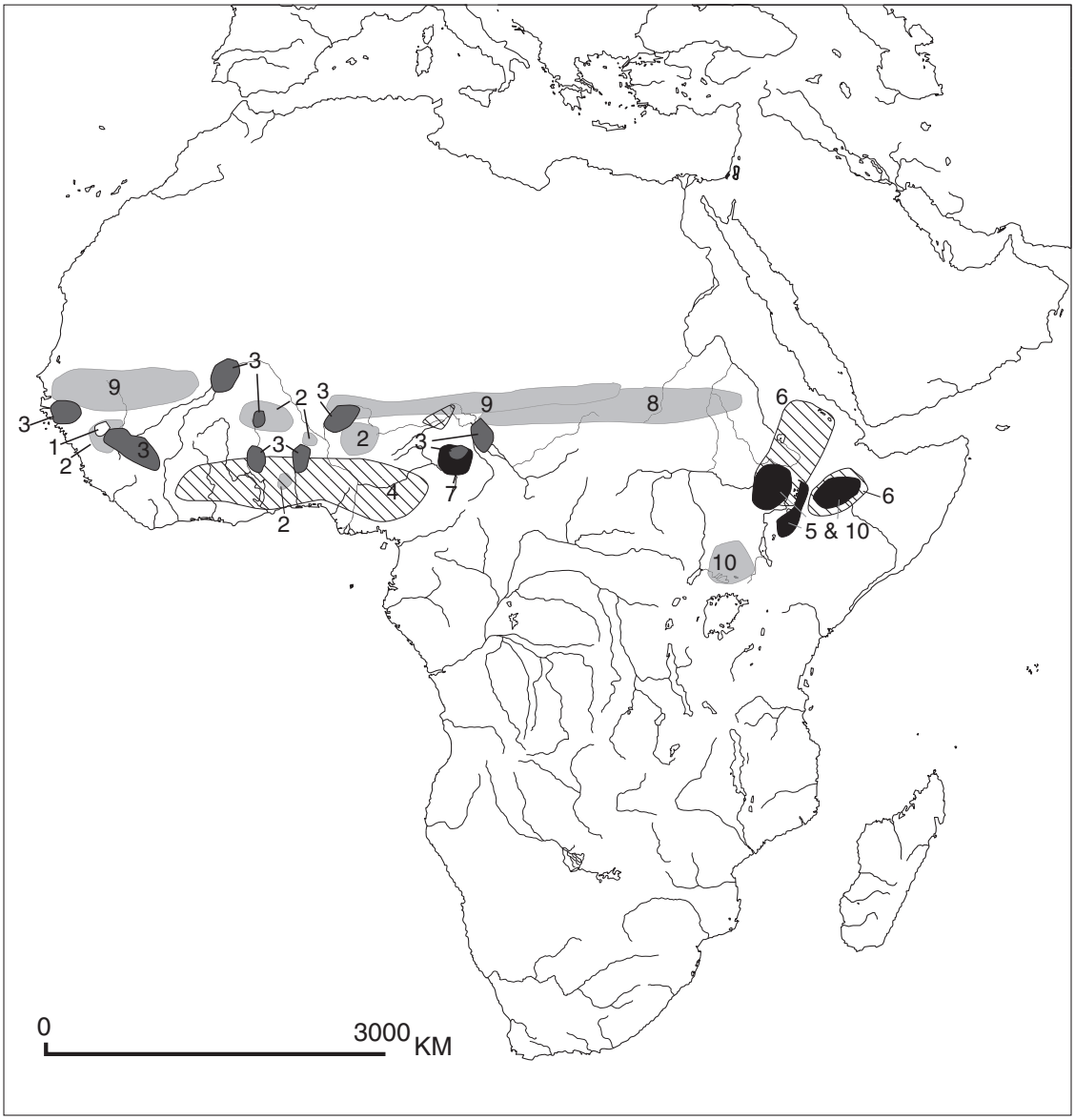

FIGURE 19.7 Farming centers across the Sahel and the forest belt in Africa during the Early to Late Holocene *(Redrawn after Harlan, J.R., 1992. Crops & Man. American Society of Agronomy, Inc., and Crop Science Society of America, Inc.)*: 1. Annual braciaria or just Braciaria; 2. Fonio millet/white fonio; 3. African rice; 4. Yam; 5. Ethiopian banana and noog (an annual herb); 6. *tef*, annual grass with small size grain; 7. Cowpea (similar to peanut from the Fabaceae family); 8. Sorghum; 9. Millet; 10. Finger millet.

(*E. coracana*), the cereal *tef* (*E. tef*), and ensete (*Musa ensete*), a banana-like plant with edible pulp at the base of the leaves.

In sum, Egypt and the Nile Valley received the products of southwestern Asia and had their impact on the Sahara and further south on the Ethiopian Neolithic societies. It is conceivable that the spread of pastoral groups and local domestication of plants in the Sahel reached Western Africa, where by about 4500 cal BP there is an independent local plants' domestication, perhaps affected by the drying desert, based on the previous hunting and gathering economy. The later developments including the spread of the Bantu people are not discussed here.

BRIEF REVIEW OF THE AMERICAS

Examining briefly the sequence of domestication centers and noncenters in the Americas must begin with Mesoamerica, where the primary domesticates determined not only the local history of social evolution but also the outcome of the historical Colombian exchange that will not be discussed in this paper (eg, Bellowod, 2013).

A major research advantage is that the population of the Americas colonized continents that had no previous human occupations. Although the debate on when, how, and where did the East Asian immigrants arrive or land, and how many times did it happen, is not fully resolved. The available evidence indicates a demographic increase during the Terminal Pleistocene and mostly during the Holocene. Recognition of this process, which allows us to identify the kind of social organizations of foragers who got acquainted with the local plant resources as well as the limited number of animals (eg, camelids, guinea pigs, and turkey). The rich Humboldt Current of the Pacific resulted in an evolved maritime economy once thought to have been the origins of South American civilization (Moseley, 1997).

Information concerning the type of foragers' dwellings and shifts in their plans by early cultivators seems to have been the same as identified in other regions of the world (eg, Flannery, 2002). In the long process that led to the establishment of cultivation that evolved to full-scale agricultural economy while keeping a major component of foraging, round huts were the first. The flimsy round structures were mostly built by females while better-built houses were the work of males as documented ethnographically. This hut type gave way to the square and rectangular buildings, together with the emergence of public areas (plazas) and intra-and intersettlements ceremonial centers (eg, Lavallée, 1995; Flannery, 2002; Quilter, 2014; Moore, 2014).

The core area of the domestication was in lowlands of Southwestern Mexico and most of the evidence for the presence of domesticates is obtained from phytoliths and starch analysis (Piperno et al., 2015; Piperno, 2011). The domesticated plants are maize (*Zea mays*), squash (*Curcurbita argyrosperma*), pumpkin (*Cucurbita pepo*), common bean (*Phaseolus vulgaris*), and chili peppers (*Capsicum annuum*) as well as fruit trees (Piperno and Pearsall, 1998; Piperno and Smith, 2012).

Dog (*Canis familiaris*) and turkey (*Meleagris gallopavo*) were the only animal domesticates that played a minor role in the diet of Central and Mesoamerican farmers (Speller et al., 2009; Bellwood, 2005). The impressive building achievements of Mesoamerican civilizations were thus created without pack animals or livestock. Dogs apparently arrived from East Asia, but Guinea pig was domesticated in the central Andes as well as the camelids.

Earlier proposals that the bottle gourds (*Lagenaria siceraria*) originated in Asia (Erickson et al., 2005) turned to be a mistaken identification (Kistler et al., 2014). The plant arrived from Africa as noted by earlier botanists. By c. 10,000 cal BP peoples inhabiting Middle America had domesticated pumpkins (Smith, 2011), and by 8700 cal BP, maize (Piperno et al., 2009; Ranere et al., 2009). The transmission of this staple southward has a date of c. 7100 cal BP in Panama (Central America) and appears later around 4500 cal BP in the southeast coast of the continent.

The archaeology of the Central Andes and the coastal plain of Southwestern America (Quilter, 2014) demonstrates, according to current research, that the process of adopting maize as a major staple food occurred in a "frog leaf" progression similarly to the spread of founder crops in Europe. The current fragmentary picture is exemplified with a few cases.

During the Early and Middle Holocene from c. 10,200 through 6300 cal BP valley inhabitants in Northern Peru adopted crop plants such as squash (*Cucurbita moschata*), peanuts (*Arachis* sp.), and cotton (*Gossypium barbadense*) (Piperno and Dillehay, 2008). In coastal Peru the earliest plant remains, ie, corn cobs, husks, stalks, and tassels, were found at c. 6700−3000 cal BP or the middle and late preceramic and early ceramic periods (Grobman et al., 2012). In Ecuador maize was cultivated and consumed as indicated by the retrieved evidence from domestic contexts at about 5300−4950 cal BP (Zarillo et al., 2008).

Agricultural techniques were evolved in Peru and Bolivia creating raised fields and large earthen platforms that prevented waterlogging and flooding, increased soil fertility, conserved moisture, and facilitated nutrient production (Erickson, 1992). Among the plants the cultivation of potato (*Solanum tuberosum*) can be traced genetically to Central Andean and Chilean landraces, exhibiting a large morphological and genetic diversity (Spooner et al., 2005).

An important grain crop is the quinoa (*Chenopodium quinoa*) originating in the Andes some 4000 years ago. It is assumed that it was domesticated at about the same time as the camelids-llama and alpaca (c. 6000−4000 cal BP) that were employed as draft animals. The domestication of the Guinea pigs occurred within the same time range.

Amazonia is currently searched for early evidence of cultivation (McMichael et al., 2012). Planting tubers such as cassava (manioc) is one of the common staples in Northern South America as well as in Central America. Cassava is a tuberous root that propagates vegetatively by cutting the stems and planting (Pujol et al., 2002). Sweet potato (*Ipomoea batatas*) is another major resource that genetically seems to have multiple origins, and was also domesticated in Central America and in South America (Roullier et al., 2013). Different trees were also food-providing sources. In sum, the South American emerging agriculture was a mixed package of seeds, roots, tubers, and trees.

Finally, as another center for local origins of agriculture we turn to Eastern North America. The archaeobotanical evidence is based on six sites, spread over a distance of 1000 km, and attributed to the Late Archaic, dated to

c. 5000−3800 cal BP (Smith, 2011 and references therein). The four open-air sites are located on riverbanks, and others are a rock-shelter, an occupation along the foot of a cliff, and a shell-midden. They were residential or seasonal habitations, sometimes with a few clay floors indicating the presence of flimsy huts. Pits, fireplaces, and discard zones produced a wealth of carbonized material. The environment was that of a forest where hickory, oak and walnut trees were exploited together with small seed plants (Smith, 2011). Two chenopods species, bottle gourd (*L. siceraria*), squash (*C. pepo*), and sunflower were domesticated along with other wild plants. The economy included hunting of white tail deer, collecting turtle and shellfish, fishing, and trapping waterfowl. Occupations are often considered as seasonal.

Other plants that were cultivated by local foragers from c. 5000−3700 cal BP were the erect knotweed (*Ploygonum erectum*), little barley (*Hordeum pusillum*), and maygrass (*Phalaris carolinian*). Maize arrived from Mexico in this region only c. 2200 cal BP. Smith (2011) considers that the subsistence strategy of these Late Archaic sites does not represent the impact of environmental downturn or a response to population packing but the attraction of the ameliorated environmental opportunities. This explanation depends on the strength of the evidence from the preceding earlier Archaic sites in the region.

DISCUSSION

The global history of agricultural origins and the ensuing developments can be viewed in a similar way to the economic successes and failures of regional adaptations of products and techniques developed during the Industrial Revolution as analyzed by recent historians. The latter is the major technological and economic change that took place in England from c.1750/1780 AD through the 19th century, according to holders of the short chronology (eg, Mokyr, 2002). Its history, when compared to the previous 12 or 11 millennia, served as a socioeconomic model for G. Childe. Fully aware of the Stone Age subdivisions, he accepted the evidence collected by contemporary European archaeologists that the Neolithic period is when the components of farming societies such as pottery, axes-adzes, built houses, and more, first appeared. He named the transition to farming as the "Neolithic Revolution" (1929, 1952). His proposal followed the original idea of the American geologist R. Pumpelly whose investigations in central Asia prompted him to suggest that the Holocene drying of this area motivated humans in oases to start cultivation. This hypothesis was later named as the "oasis theory" that correlated a climatic change with the onset of agriculture.

Childe followed A. Toynbee, a 19th century historian, and others in comparing the course of the historically recorded changes in Britain to prehistoric western Asia, often referred to as the Near East. While the study of the Industrial Revolution is based on a wealth of quantitative information concerning demographics, new machinery, labor movements, and more, it is not the same for the study of the prehistoric "revolution." The emergence of agro-pastoral societies took a longer time to accomplish in the centers, and its interpretation depends on the archaeological reports that document the social and economic changes along with the development of religious and social domains. The documented changes of the Neolithic Revolution, which occurred in a relatively fast rate, measured in evolutionary scale, can be summarized archaeologically by employing ethnographic data (eg, Flannery and Marcus, 2012; Kelly, 2013). Together with the recorded evidence concerning the Industrial Revolution the main components are as follows (eg, Mokyr, 2002; Deane, 1979; Mathias and Davis, 1989; Price and Feinman, 2010):

1. The onset of cultivation by foragers was a systematic application of practical wisdom passed on through the "social memory" of a given social entity ("tribe"). Implementing the in-depth knowledge of life cycles of plants and patterns of behavior of domesticable wild animals facilitated repeated trials in the production of plant food and animal husbandry. Steady annual cultivation emerged in sedentary or semisedentary hamlets and villages. Dwellings changed from rounded huts to rectangular buildings in the course of this slow but significant process.
2. The realization that the production of stored surplus beyond the annual needs of a family or a band assisted in gaining power over nonfarming groups and consequently enabled the geographic expansion of budding-off communities. These spread into new arable lands, mostly in river valleys, as well as pastures in hilly landscape and later in steppic and semidesert environments.
3. The long-distance routes that facilitated exchange or barter of precious commodities were employed for the transmissions of technical knowledge and agricultural products resulting in the emergence of wealthier families, forming the local elite. It motivated additional traveling into other lands by using sea vessels and/or river transport. Taking over areas occupied by hunter-gatherers was the inevitable outcome of the need for extra arable land.
4. Transfer of labor from activities related to the production of primary staple food to the production of special goods for exchange and trade with neighboring as well

as further-away communities marked the cultural achievements of the Early Neolithic period (c. 11,700–8200 cal BP) in the Fertile Crescent. Richer village communities allowed for training and hosting mobile, skilled artisans, and benefited from their products for local use and exchange.

5. Attributing social power to individuals who could serve the community as leaders, organizers, and negotiators with other communities whether close (belonging to the same tribe) or beyond their controlled territory, was an additional step in social evolution. The emergence of "big men" or "chiefs," whether or not in control of the religious domain, facilitated the enhancement of social cohesion based on the original Paleolithic concept of "us" and "them."
6. Earlier aggregation sites, whether in a village or in a special geographic space, allowed for establishing ceremonial centers, adding an extra level for organized religious activities.

Similar to the debates concerning the roots and reasons for the onset of the Industrial Revolution, there are disagreements concerning the why question as regards the onset of the agricultural revolution. We phrase it as "what triggered the Neolithic or Agricultural Revolution?" Supporters of the various hypotheses employ the archaeological records for their own interpretations by examining different regions in the world to reveal the processes involved in the so-called transition from foraging to farming. This chapter does the same. The region best documented, in spite of certain gaps, is the Levant. Without getting entangled with current views of various scholars that argue for the use of Broad Spectrum, Niche Construction, or Optimal Foraging theories (eg, Smith, 2011; Zeder, 2015; Gremillon et al., 2014), or even a "No-model Model" (Harlan, 1992), I will first stress the common observations for the emergence of the various centers and later the noncenters.

An ecological approach to why people cultivate places a considerable weight on the available regional geographic features and the naturally available plant and animal resources. The Mediterranean climatic and vegetation belt that stretches around the basin of this sea is the largest of its kind in the world. Its eastern periphery, known as Southwestern Asia or the Near East, is the richest in all components. As clearly stressed by Diamond (1997, 2012), on a global scale, it is the most diverse in terms of topographic features, cold and rainy winters and dry summers, domesticable plants, and animal species. Indeed, the evidence for early cereal cultivation and animal domestication raises the question of why did it happened in the Levant.

The answers are sought in the ecological advantages. An earlier study proposed the relationships between the wild cereal grain size and human selection (Bar-Yosef and Kislev, 1989). Diamond (1997, 2012) cites the in-depth study of Blumler (1992) that compared the size of seeds among plant resources in different regions. Blumler found that 56 large seed species are common in the Mediterranean region of Western Asia and Southern Europe that outnumber any of the large seeds in similar vegetation associations in the world. While this observation is correct, in other areas, such as Northern China, smaller grain species such as the broomcorn and foxtail millet, were domesticated. The cause therefore for successful cultivation on a worldwide scale should be sought not only in the ecological advantages but in the local social contexts and rate of innovation among foragers.

In searching for why did the cultivation of various plants and the domestication of animals, where the adequate progenitors were present, began some 15–12 millennia ago, we need to examine the known behavior of Late Pleistocene foragers.

The current literature on hunter-gatherers indicates that the need for food is the main cause of either short- or long-distance mobility employing residential or logistical moves, or the combinations of both (Binford, 2001; Kelly, 2013). If we add to this the knowledge kept in the social memory, human ability for positive foresights, as well as making mistakes, then the recognition of acute food stress events may result in short- or long-term planning. Pressures are variable due to ecological and social stresses. An abrupt climatic crisis such as a series of drought years in the Mediterranean basin and increasing relative densities of other foragers' bands competing for the same sources may result in increasing sense of territoriality (property ownership), changing subsistence strategies by intensification, as well as competition and physical conflicts.

Circumstances of alternating situations of "plenty" and "scarce" motivated various kinds of human interactions with their environments. The Paleolithic modes of procurements changed, as witnessed archaeologically and summarized earlier, during the Late Pleistocene and the Holocene across the continents. Why? In the detailed recorded cases the archaeological data indicate situations of social pressures that required restricted anticipated mobility, semisedentism and/or full sedentism, and a certain degree of territorial control. During most of the Paleolithic sedentism was practiced as a cyclical, temporary solution. Only from the Late Pleistocene (c. 23,000–11,700 cal BP) it became the sole successful strategy in the Levant, and in areas such as North China and South China. With the lack of social covenant that respects property rights across a large area the adherence to cultivation of the best available edible plants and fruit trees, even on a relatively small scale, required giving up residential mobility and construct permanent dwellings. In addition, readiness for unpredictable conflicts was needed. Apparently, sedentism (or semisedentism) was a tactical solution adopted by the pioneers of cultivation and resulted in the common acceptance of new social rules (eg, Flannery and Marcus,

2012). The ensuing demographic pressures are now seen as the major factor in the demand for land (eg, Ellis et al., 2013). However, the survival of a family who decided to quit or was unlucky to be expelled from its village society was secured when an alternative place, a refuge was available. Genetics recorded the case of farmers who returned to being hunter-gatherers in Thailand's forests (Oota et al., 2005).

In several regions cultivation and animal domestication (wherever it was an option) succeeded. In others it failed. An overview of the centers provides the impression that the original investments resulting in the domestication of founder crops were a success. The same is true concerning the domestication of goat, sheep, pig, and cattle. Within several millennia rapid human population growth characterized Southwestern Asia (eg, Bouquet-Appel, 2011), and this process repeated itself in every center and noncenter alike (papers in Bouquet-Appel and Bar-Yosef, 2008). But we should note that when archaeological records are sufficiently detailed, short failures are detected such as in the Levant around c. 10,200 cal BP (eg, Borrell et al., 2015). This event is better marked in the more arid areas in the short occupational gap between the PPNA and PPNB periods (Goring-Morris and Belfer-Cohen, 2011; Belfer-Cohen and Goring-Morris, 2011).

Summing up the first steps of cultivation and plant domestication in the Levant I briefly mention the arguments presented earlier (section The Fertile Crescent). The debate centers on how long it took the fields of Neolithic farmers to be dominated by fully domesticated cereals. The options are two to three centuries (eg, Hillman and Davies, 1992; Abbo et al., 2013) or a longer process of over a millennium or two (Willcox, 2012; Fuller, 2007). In addition, there were also the unsuccessful trials with wild oat, rambling vetch, rye, and wild black lentil (eg, Weiss et al., 2006; Abbo et al., 2013).

The argument for a short time of domestication in the Levant is theoretically derived from Zipf's "law of least effort" and Levi-Straus's statement of human capacities for conscious selection (Abbo et al., 2013). However, this approach does not take into account that human decisions do not conform to the logic of economic preferences as shown by "game theory" (Kahneman, 2003).

Molecular biology plays a role in investigating the prehistory of agriculture by analyzing the living descendants of the plants such as wheat, barley, rice, and maize as well as that of domesticated animals (dogs, goats, sheep, pig, cattle, and more). However, without direct archaeological evidence, as already stressed by J. Harlan (1992) it is impossible to correlate the phylogenetic analyses with a historical sequence, even with the estimated age for the genetic bottlenecks of the domesticated plants. Paleogenetics do a better job concerning animals as the analysis is based on archaeological samples. However, with the plants this type of investigation is still in its infancy (Gept, 2014). Humans, once they started managing and manipulating plants and animals, never stopped innovating and thus the same plants and animals passed through more than one mutational event, and introgression of genes from their wild relatives, either accidentally or intentionally. Genetic analysis, when done through the use of a mixture of statistical methods, including the computational analysis named "Approximate Bayesian Computation," clarifies and stresses the single and earlier domestication events (Gerbault et al., 2014). Together with the archaeological evidence that produces the radiocarbon dates of the domesticated animals and plants it allows us to trace the dispersal routes discussed earlier.

Today's records demonstrate that there were just a few centers and numerous noncenters. Once agriculture was established in one region, interactions by land and sea with other locations initiated the patterns of exchanges of plants and animals such as the later historical Colombian exchange (eg, Crosby, 1993; Bellwood, 2013). This process began during the Holocene but was enhanced after 8000 or 7000 cal BP. A. Sherratt (1981) labeled the improved and enriched agricultural package of this time as the "Secondary Products Revolution." Due to space limitations this interesting phase in the development of the foundations of modern agro-pastoral societies is not discussed. Instead, I have tried to demonstrate the nature of the "origins" when hunter-gatherers societies became farmers by cultivating selected plants, tending certain fruit trees, planting tubers, constructing round dwellings, and establishing sedentary communities and property rights over a given territory. This process repeated itself in Eurasia, Africa, and the Americas demonstrating in its incipient phase similar human behavior resulting in a responsibility for a continuum from foraging to farming. The tipping point that demarcates the separation between the two strategies is when most of the diet is based on the founder crops and herding. Small-scale foraging continues by farmers. I also suggest that the archaeological remains that reflect a major change in energy expenditure when constructing and maintaining houses and ceremonial centers should be considered as a major marker, whether all plants are fully domesticated or not. In addition to managing cultivation and storage, exerting territorial control, increasing in long-distance exchanges, and the presence of mobile artisans are the cumulative expressions of what the term Neolithic Revolution means. Implicitly, describing this process as "Neolithization" is what is seen as the main cause for the Anthropocene. Niche Construction, the feedback dynamic interaction between humans and their environments, is what several decades ago was a research topic resulting in two major volumes entitled "Man's Role in Changing the Face of the Earth" (Thomas, 1955).

Preindustrial societies are considered as conducting ecosystem engineering directed toward wild plants and animals, and therefore are involved in subsistence and habitat improvements (Smith, 2011). These relationships

were probably a cyclical phenomenon during the Paleolithic but drastically changed during the Late Pleistocene and the Holocene in the respective centers and noncenters. Relative demographic pressures during this period in Eurasia and Africa and during the Holocene in the Americas motivated humans to adopt similar solutions. Once cultivation and sedentism were established as a permanent subsistence strategy, it became the tipping point in human evolution. Retractions and failures probably occurred in more than one case during this long-term process. Those that succeeded determined the current history of our planet.

ACKNOWLEDGMENTS

I thank M. Tibayrenc and F. Ayala for inviting me to contribute this chapter. I did not intend to cover the entire world but as I continued to build the case, in particularly for plant domestication, I felt the need for additional information to be summarized to clarify my position on the issue of how foragers became farmers. I am grateful to A. Belfer-Cohen (Hebrew University), D. Bar-Yosef Mayer (Steinhardt Museum of Natural History, Tel-Aviv University), E. Weiss (Bar-Ilan University), and D.J. Cohen (Department of Anthropology, National Taiwan University, Taiwan) for commenting on and copyediting earlier drafts of this manuscript. All shortcomings, omissions, and mistakes are mine.

REFERENCES

Abbo, S., Lev-Yadun, S., Gopher, A., 2010. Agricultural origins: centers and noncenters; a near eastern reappraisal. Critical Reviews in Plant Sciences 29, 317–328.

Abbo, S., Zezak, I., Schwartz, E., Lev-Yadun, S., Kerem, Z., Gopher, A., 2008. Wild lentil and chickpea harvest in Israel: bearing on the origins of Near Eastern farming. Journal of Archaeolgical Science 35, 3172–3177.

Abbo, S., Lev-Yadun, S., Gopher, A., 2011. Origin of Near Eastern Plant Domestication: Homage to Claude Levi-Strauss and "La Pensée Sauvage". Genetic Resources and Crop Evolution 58, 175–179.

Abbo, S., Lev-Yadun, S., Gopher, A., 2012. Plant domestication and crop evolution in the Near East: on events and processes. Critical Reviews in Plant Sciences 31 (3), 241–257.

Abbo, S., Pinhasi van-Oss, R., Gopher, G., Saranga, Y., Ofner, I., Peleg, Z., 2013. Plant domestication versus crop evolution: a conceptual framework for cereals and grain legumes. Trends in Plant Science 19, 351–360.

Albright, W.F., 1957. From the Stone Age to Christianity: Monotheism and the Historical Process. John Hopkins Press, Baltimore.

Amblard, S., Pernés, J., 1989. The identification of cultivated pearl millet (Pennisetum) amongst plant impressions on pottery from Oued Chebbi (Dhar Oualata, Mauritania). The African Archaeological Review 7, 117–126.

Ammerman, A.J., Cavalli-Sforza, L.L., 1984. The Neolithic Transition and the Genetics of Populations in Europe. Princeton University Press, Princeton.

Anderson, M.K., Wholgemuth, E., 2012. Californian Indian proto-agriculture: its characterization and legacy. In: Gepts, P., Famula, T.R., Bettinger, R.L., et al. (Eds.), Biodiversity in Agriculture. Cambridge University Press, pp. 190–224.

Arbuckle, B.S., Whitcher Kansa, S., Kansa, E., et al., 2014. Data sharing reveals complexity in the westward spread of domestic animals across Anatolia. PLoS One (6), e99845 doi:10371/journal.pone.0099845.

Asersea, A.,A., Räsänena, L.A., Assefa, F., et al., 2012. Phylogeny and genetic diversity of native rhizobia modulating common bean (*Phaseolus vulgaris* L.) in Ethiopia. Systematic and Applied Microbiology 35, 120–131.

Asouti, E., Fuller, D.Q., 2012. From foraging to farming in the southern Levant: the development of epipalaeolithic and pre-pottery Neolithic plant management strategies. Vegetation History and Archaeobotany 21, 169–182.

Auffrey, J.C., Tchernov, E., Nevo, E., 1989. Origine de commensalisme de la souris domestique (Mus musculus domesticus) vis-a-vis l"homme. Comptes Rendus de l'Académie des Sciences 307 (Serie III), 517–522.

van Andel, T., Runnels, C.N., 1995. The earliest farmers in Europe. Antiquity 69, 481–500.

Bar-Oz, G., 2004. Epipalaeolithic Subsistence Strategies in the Levant: A Zooarchaeological Perspective. American School of Prehistoric Research Monograph Series, Brill, Boston.

Bar-Yosef, O., 2011. Climatic fluctuations and early farming in West and East Asia. Current Anthropology 52 (S4), S175–S193.

Bar-Yosef, O., 2001. From sedentary foragers to village hierarchies: the emergence of social institutions. In: Runciman, G. (Ed.), The Origin of Human Social Institutions. Oxford University Press, pp. 1–38.

Bar-Yosef, O., 2013. Nile Valley-Levant interactions: an eclectic review. In: Shirai, N. (Ed.), Neolithization of Northeastern Africa, Studies in Early Near Eastern: Production, Subsistence, & Environment, vol. 16. Ex Oriente, Berlin, pp. 237–247.

Bar-Yosef, O., 2014. Southeast Turkish Neolithic: a view from the southern Levant. In: Özdoğan, M., Basgelen, N., Kuniholm, P. (Eds.), The Neolithic of Turkey, 6. Archaeology and Art Publications, Istanbul, pp. 293–320.

Bar-Yosef, O., Kislev, M.E., 1989. Early farming communities in the Jordan Valley. In: Harris, D.R., Hillman, G.C. (Eds.), Foraging and Farming: The Evolution of Plant Exploitation. Hyman Unwin, London, pp. 632–642.

Bar-Yosef, O., Valla, F. (Eds.), 1991. The Natufian Culture in the Levant. International Monographs in Prehistory, Ann Arbor.

Bar-Yosef, O., Eren, M.I., Yuan, J., Cohen, D.J., Li, Y., 2012. Were bamboo tools made in prehistoric Southeast Asia? An experimental view from South China. Quaternary International 269, 9–21.

Bar-Yosef, O., Valla, F. (Eds.), 2013. Natufian Foragers in the Levant: Terminal Pleistocene Social Changes in Western Asia. International Monographs in Prehistory, Ann Arbor.

Barker, G., Janowski, M. (Eds.), 2011. Why Cultivate? Anthropological and Archaeological Approaches to Foraging-farming Transitions in Southeast Asia. McDonald Institute Monographs, Cambridge University.

Baker, O., Lee, O.Y.-C., Wu, H.T., et al., 2015. Human tuberculosis predates domestication in ancient Syria. Tuberculosis 95, S4–S12.

Balaresque, P., Bowden, G.R., Adams, S.M., et al., 2010. A predominantly Neolithic origin for European paternal lineages. PLoS Biology 8 (1), e1000285. http://dx.doi.org/10.1371/journal.pbio.1000285.

Barton, L., Brantingham, P.J., Ji, D., 2007. Late Pleistocene climate change and Paleolithic cultural evolution in northern China: Implications from the Last Glacial Maximum. In: Madsen, D.B., et al. (Eds.), Late Quaternary climate change and human adaptation in arid China. Elsevier, pp. 105–128.

Barton, L., Newsome, S.D., Chen, F.-H., et al., 2009. Agricultural origins and the isotopic identity of domestication in northern China. Proceedings of the National Academy of Sciences of the United States of America 106, 5523–5528.

Belfer-Cohen, A., 1995. Rethinking social stratification in the Natufian culture: the evidence from burials. In: Campbell, S., Green, A. (Eds.), The Archaeology of Death in the Ancient Near East. Oxbow Monograph 51, Oxford, pp. 9–16.

Belfer-Cohen, A., Bar-Yosef, O., 2010. First things first: abstract & figurative artistic expressions in the Levant. In: Bahn, P. (Ed.), An Enquiring Mind: Studies in Honor of Alexander Marshack. American School of Prehistoric Research Monographs Series, Oxbow: Oxford & Oakville, pp. 3–17.

Belfer-Cohen, A., Goring-Morris, N.A., 2011. Becoming farmers: the inside story. Current Anthropology 52 (Suppl. 4), S209–S220.

Bellwood, P., 2005. First Farmer: The Origins of Agricultural Societies. Blackwell Publishing.

Bellwood, P., 2013. First Migrants: Ancient Migrations in Global Perspective. Wiley Blackwell.

Benz, M., Deckers, K., Rössner, C., et al., 2015. Prelude to village life. Environmental data and building traditions of the epipalaeolithic settlement at Körtik Tepe, Southeastern Turkey. Paléorient 41 (2), 9–30.

Bestel, S., Crawford, G.W., Liu, L., et al., 2014. The evolution of millet domestication, middle Yellow River region, north China: evidence from charred seeds at the late upper Paleolithic Shizitan locality 9 site. Holocene 24, 261–265.

Bettinger, R.L., Barton, L., Richerson, P.J., et al., 2007. The transition to agriculture in Northwestern China. In: Madsen, D.B., Chen, F.H., Gao, X. (Eds.), Late Quaternary Climate Change and Human Adaptation in Arid China. Elsevier, pp. 83–101.

Binford, L.R., 1981. Bones: Ancient Men and Modern Myths. Academic Press, New York.

Binford, L.R., 2001. Constructing frames of reference: An Analytical Method for Archaeological Theory Building Using Ethnographic and Environmental data sets. University of California Press.

Bird, R., 1999. Cooperation and conflict: the behavioral ecology of the sexual division of labor. Evolutionary Anthropology 8, 65–75.

Blumler, M.A., 1992. Seed Weight and Environment in Mediterranean-type Grasslands in California and Israel. University of California, Berkeley (Ph.D. thesis).

Bouquet-Appel, J.P., Bar-Yosef, O. (Eds.), 2008. The Neolithic Demographic Transition and its Consequences. Springer.

Bouquet-Appel, J.-P., 2011. The agricultural demographic transition and after agriculture inventions. Current Anthropology 52, S497–S-510.

Borrell, F., Junno, A., Barceló, J.A., 2015. Synchronous environmental and cultural change in the emergence of agricultural economies 10,000 years ago in the Levant. PLoS One 10 (8), e0134810. http://dx.doi.org/10.1371/journal.pone.0134810.

Brock, F., Higham, T., Ditchfield, P., Ramsey, C.B., 2010. Current pretreatment methods for AMS radiocarbon dating at the oxford radiocarbon accelerator unit (ORAU). Radiocarbon 52, 103–112.

Brown, T.A., Jones, M.K., Powell, W., Allaby, G., 2008. The complex origins of domesticated crops in the fertile crescent. Cell 24 (2), 103–109.

Butzer, K., 2015. *Anthropocene* as an evolving paradigm. Holocene 25 (10), 1539–1541.

Le Bailly, M., Harter, S., Bouchet, F., 2003. A l'interface de la biologie et de l'archéologie: la Paléoparasitologie. Archéopages 11, 12–17.

Le Bailly, M., Leuzinger, U., Schlichtherle, H., Bouchet, F., 2005. *Diphyllobothrium*: Neolithic parasite? Journal of Parasitology 91 (4), 957–959.

Caracuta, V., Barzilai, O., Khalaily, H., et al., 2015. The onset of faba bean farming in the Southern Levant. Scientific Reports 5, 14370. http://dx.doi.org/10.1038/srep14370, 1–9.

Cauvin, J., 2000. The Birth of the Gods and the Origins of Agriculture. Cambridge University Press, Cambridge.

Cavalli-Sforza, L.L., Feldman, M.W., 2003. The application of molecular genetic approaches to the study of human evolution. Nature Genetics 33 (Suppl.), 266–274.

Childe, G.V., 1929. The Danube in Prehistory. Clarendon Press, Oxford.

Childe, V.G., 1952. New Light on the Most Ancient Near East. Routledge & Paul, London.

Cohen, D.J., 2011. The beginnings of agriculture in China: a multiregional view. Current Anthropology 52, S273–S293.

Collard, M., Buchanan, B., O'Brien, M.J., 2013. Population size as an explanation for patterns in the Paleolithic archaeological record: more caution is needed. Current Anthropology 54 (S8), S388–S396.

Colledge, S., 2002. Identifying pre-domestication cultivation in the archaeobotanical record using multivariate analysis: presenting the case for quantification. In: Cappers, R.T.J., Bottema, S. (Eds.), The Dawn of Farming in the Near East. Ex Oriente, Berlin, pp. 141–152.

Colledge, S., Conolly, J., 2010. Reassessing the evidence for the cultivation of wild crops during the younger Dryas at Tell Abu Hureyra, Syria. Environmental Archaeology 15, 124–138.

Collins, D.A., McGrew, W.C., 1988. Habitats of three groups of chimpanzees (*Pan troglodytes*) in western Tanzania compared. Journal of Human Evolution 17, 553–0594.

Cordain, L., Hickey, M.S., Kim, K., 2012. Malaria and rickets represent selective forces for the convergent evolution of adults lactase persistence. In: Gepts, P., Famula, T.R., Bettinger, R.L., et al. (Eds.), Biodiversity in agriculture. Cambridge University Press, pp. 299–308.

Crawford, G.W., 2008. The Jomon in early agriculture discourse: issues arising from Matsui, Kanehara and Pearson. World Archaeology 40 (4), 445–465.

Crawford, G.W., 2011. Advances in understanding early agriculture in Japan. Current Anthropology 52, S331–S345.

Crosby, A., 1993. Ecological Imperialism: The Biological Expansion of Europe, 900–1900. Cambridge University Press, Cambridge.

Cucchi, T., Hulme-Beaman, A., Yuan, J., Dobney, K., 2011. Early Neolithic pig domestication at Jiahu, Henan Province, China: clues from molar shape analyses using geometric morphometric approaches. Journal of Archaeological Science 38, 11–22.

De Candolle, A.D., 1884. Origin of Cultivated Plants. Kegan Paul, Trench.

Dahlberg, F. (Ed.), 1981. Woman the Gatherer. Yale University Press, New Haven, pp. 75–120.

Davis, S.J.M., Valla, F.R., 1978. Evidence for domestication of the dog 12,000 years ago in the Natufian of Israel. Nature 276, 608–610.

Deane, P., 1979. The First Industrial Revolution, second ed. Cambridge University Press, Cambridge.

Deng, Z.X., Qin, L., Gao, Y., et al., 2015. From early domesticated rice of the middle Yangtze basin to millet, rice and wheat agriculture: archaeobotanical macro-remains from Baligang, Nanyang basin, Central China (6700–500 BC). PLoS One 10 (10), e0139885. http://dx.doi.org/10.1371/journal.pone.0139885.

Denham, T., 2011. Early agriculture and plant domestication in new Guinea and island southeast Asia. Current Anthropology 52, S379–S395.

Diamond, J., 1997. Guns, Germs, and Steel: The Fates of Human Societies. W.W. Norton & Company.

Diamond, J., 2012. The local origins of domestication. In: Gepts, P., Famula, T.R., Bettinger, R.L., et al. (Eds.), Biodiversity in Agriculture. Cambridge University Press, pp. 9–20.

Eitam, D., Kislev, M., Karty, A., Bar-Yosef, O., 2015. Experimental barley flour production in 12,500-year-old rock-cut mortars in southwestern Asia. PLoS One 1–10. http://dx.doi.org/10.1371/journal.pone.0133306.

Ellis, E.C., Kaplan, J.O., Fuller, D.Q., et al., 2013. Used planet: a global history. Proceedings of the National Academy of Sciences of the United States of America 110, 7978–7985.

Erickson, C.L., 1992. Prehistoric landscape management in the Andean highlands: raised field agriculture and its environmental impact. Population and Environment 13, 285–300.

Erickson, D.L., Smith, B.D., Clarke, S.A.C., et al., 2005. An Asian origin for a 10,000-year-old domesticated plant in the Americas. Proceedings of the National Academy of Sciences of the United States of America 102, 18315–18320.

Ervynck, A., Dobney, K., Hong, O.H., Meadow, R., 2001. Born free? New evidence for the status of *Sus scrofa* at Neolithic Çayönü Tepesi (southeastern Anatolia, Turkey). Paléorient 27 (2), 47–73.

Evershed, R.P., Payne, S., Sherratt, A.G., Copley, M.S., et al., 2008. Earliest date for milk use in the Near East and southeastern Europe linked to cattle herding. Nature 455, 528–531.

Fullagar, R., Field, J., Denham, T., Lentfer, C., 2006. Early and mid Holocene tool-use and processing of taro (*Colocasia esculenta*), yam (*Discorea* sp.) and other plants at Kuk Swamp in the highlands of Papua New Guinea. Journal of Archaeological Science 33, 595–614.

Flannery, K.V., 2002. The origins of the village revisited: from nuclear to extended households. American Antiquity 67, 417–433.

Flannery, K.V., 1969. Origins and ecological effects of early domestication in Iran and the Near East. In: Ucko, P.J., Dimbleby, G.W. (Eds.), The Domestication and Exploitation of Plants and Animals. Duckworth, London, pp. 73–100.

Flannery, K., Marcus, J., 2012. The Creation of Inequality. How Our Prehistoric Ancestors Set the Stage for Monarchy, Slavery, and Empire. Harvard University Press, Cambridge.

Fort, J., 2012. Synthesis between demic and cultural diffusion in the Neolithic transition in Europe. Proceedings of the National Academy of Sciences of the United States of America 109, 18669–18673.

Fuller, D.Q., 2007. Contrasting patterns in crop domestication and domestication rates: recent archaeological insights from the Old World. Annals of Botany 100, 903–924.

Fuller, D.Q., 2010. An emerging paradigm shift in the origins of agriculture. World Anthropology 17 (1), 8–12.

Fuller, D.Q., 2011. Finding plant domestication in the Indian subcontinent. Current Anthropology 52, S347–S362.

Fuller, D.Q., Rowlands, M., 2011. Ingestion and food technologies: maintaining differences over the long-term in West, South and East Asia. In: Wilkinson, T.C., Sherratt, A., Bennett, J. (Eds.), Interweaving Worlds: Systematic Interactions in Eurasia, 7th to 1st Millennia BC. Oxbow Books, Oxford, pp. 37–60.

Fuller, D.Q., Korisettar, R., Venkatasubbaiah, P.C., Jones, M.K., 2004. Early plant domestications in southern India: some preliminary archaeobotanical results. Vegetation History and Archaeobotany 13, 115–129.

Fuller, D.Q., Qin, L., Zheng, Y., et al., 2009. The domestication process and domestication rate in rice: spikelet bases from the lower Yangtze. Science 323, 1607–1610.

Fuller, D.Q., Willcox, G., Allaby, R.G., 2011. Cultivation and domestication had multiple origins: arguments against the core area hypothesis for the origins of agriculture in the Near East. World Archaeology 43, 628–652.

Fuller, D.Q., Willcox, G., Allaby, R.G., 2012. Early agricultural pathways: moving outside the "core area" hypothesis in Southwest Asia. Journal of Experimental Botany 63, 617–633.

Galibert, F., Quignon, P., Hitte, C., André, C., 2011. Toward understanding dog evolutionary and domestication history. Comptes Rendus Biologies 334, 190–196.

Gallego Llorente, M., Jones, E.R., Eriksson, A., et al., 2015. Ancient Ethiopian genome reveals extensive Eurasian admixture throughout the African continent. Science 350, 820–822.

Garrard, A.N., Byrd, B.F., 2013. Beyond the Fertile Crescent: Let Palaeolithic and Neolithic Communities of the Jordanian Steppe, vol. 1. Oxbow Books, Oxford & Oakville.

Gautier, A., 2001. The early to late Neolithic Archaeofaunas from Nabta and Bir Kiseiba. In: Wendorf, F., Schild, R., Associates (Eds.), Holocene Settlement of the Egyptian Sahara, The Archaeology of Nabta Playa, vol. 1. Plenum, New York, pp. 609–635.

Gept, P., 2014. Domestication of plants. In: Encyclopedia of Agriculture and Food Systems, vol. 2. Elsevier, San Diego, pp. 474–486.

Gerbault, P., Liebert, A., Itan, Y., et al., 2011. Evolution of lactase persistence: an example of human niche construction. Philosophical Transactions of the Royal Society B: Biological Sciences 366, 863–877. http://dx.doi.org/10.1098/rstb.2010.0268.

Gerbault, P., Allaby, R.G., Boivin, N., et al., 2014. Storytelling and story testing in domestication. Proceedings of the National Academy of Sciences of the United States of America 111, 6159–6164.

Goren-Inbar, N., Sharon, G., Melamed, Y., Kislev, M., 2002. Nuts, nut cracking, and pitted stones at Gesher Benot Ya'aqov, Israel. Proceedings of the National Academy of Sciences of the United States of America 99, 2455–2460.

Goren-Inbar, N., Melamed, Y., Zohar, I., et al., 2014. Beneath still waters – multistage aquatic exploitation of *Euryale ferox* (Salisb.) during the Acheulian. Internet Archaeology 37.

Goring-Morris, A.N., Belfer-Cohen, A., 2011. Neolithization processes in the Levant: the outer envelope. Current Anthropology 52, S195–S208.

Gourichon, L., Helmer, D., 2008. Etude archeozoologique de Mureybet. In: Ibanez, J.J. (Ed.), Le site neolithique de Tell Mureybet (Syrie du Nord). En hommage a Jacques Cauvin, pp. 115–228. BAR International series 1843.

Grobmana, A., Duccio Bonavia, D., Dillehay, T.D., et al., 2012. Preceramic maize from Paredones and Huaca Prieta, Peru. Proceedings of the National Academy of Sciences of the United States of America 109 (5), 1755–1759.

Gremillion, K.J., Barton, L., Piperno, D.R., 2014. Particularism and the retreat from theory in the archaeology of agricultural origins. Proceedings of the National Academy of Sciences of the United States of America 111, 6171–6177.

Grosman, L., Munro, N., Abadi, I., et al., 2016. Nahal Ein Gev II, a late Natufian community at the sea of Galilee. PLoS One 11 (1), 1–32. http://dx.doi.org/10.1371/journal.pone.0146647.

Gross, B.L., Zhao, Z., 2014. Archaeological and genetic insights into the origins of domesticated rice. Proceedings of the National Academy of Sciences of the United States of America 111, 6190–6197.

Haak, W., Lazaridis, I., Patterson, N., et al., 2015. Massive migration from the steppe was a source for Indo-European languages in Europe. Nature 522, 207–211.

Hammer, K., 1984. Das Domestikationssyndrom. Kulturpflanze 32, 11–34.

Hardy, K., Blakeney, T., Copeland, L., et al., 2009. Starch granules, dental calculus and new perspectives on ancient diet. Journal of Archaeological Science 36, 248–255.

Harlan, J.R., 1971. Agricultural origins: centers and noncenters. Science 174, 468–473.

Harlan, J.R., 1992. Crops & Man. American Society of Agronomy, Inc., and Crop Science Society of America, Inc.

Harlan, J.R., 1995. The Living Fields. Our Agricultural Heritage. Cambridge University Press.

Harris, D.R., 2007. Agriculture, cultivation and domestication: exploring the conceptual framework of early food production. In: Denham, T., Iriarte, J., Vrydaghs, L. (Eds.), Rethinking Agriculture: Archaeological and Ethnoarchaeologiucal Perspectives. Left Coast Press, Walnut Creek, California, pp. 15–35.

Hartman, G., Bar-Yosef, O., Brittingham, A., Grosman, L., Munro, N.D., 2016. Hunted gazelles evidence cooling, but not drying, during the Younger Dryas in the southern Levant. Proceedings of the National Academy of Sciences of the United States of America 113, 3997–4002.

Henry, A.G., Brooks, A.S., Piperno, D.R., 2011. Microfossils in calculus demonstrate consumption of plants and cooked foods in Neanderthal diets (Shanidar III, Iraq; Spy I and II, Belgium). Proceedings of the National Academy of Sciences of the United States of America 108, 486–491.

Hershkovitz, I., Donoghue, H.D., Minnikin, D.E., Besra, G.S., Lee, O.Y., Gernaey, A.M., Galili, E., Eshed, V., Greenblatt, C.L., Lemma, E., Bar-Gal, G.K., Spigelman, M., 2008. Detection and molecular characterization of 9,000-year-old *Mycobacterium tuberculosis* from a Neolithic settlement in the eastern Mediterranean. PLoS One 3, e3436.

Higham, C.F.W., 2015. Debating a great site: Ban non Wat and the wider prehistory of Southeast Asia. Antiquity 89 (347), 1211–1220.

Hodgson, J.A., Mulligan, C.J., Al-Meeri, A., Raum, R.L., 2014. Early Back-to-Africa migration into the horn of Africa. PLoS Genetics 10 (6), e1004393. http://dx.doi.org/10.1371/journal.pgen.1004393.

Hillman, G.C., 2000. Abu Hureyra 1: the Epipalaeolithic. In: Moore, A.M.T., Hillman, G.C., Legge, A.J. (Eds.), Village on the Euphrates: From Foraging to Farming at Abu Hureyra. Oxford University Press, Oxford, pp. 327–399.

Hillman, G.C., Davies, M.S., 1990. Measured domestication rates in wild wheats and barely under primitive cultivation, and their arcaheological implications. Journal of World Prehistory 4, 157–222.

Hillman, G.C., Hedges, R., Moore, A., et al., 2001. New evidence of Lateglacial cereal cultivation at Abu Hureyra on the Euphrates. The Holocene 11, 383–393.

Hodder, I., 2007. Catalhöyük in the context of the middle eastern Neolithic. Annual Review of Anthropology 36, 105–120.

Hole, F. (Ed.), 1987. The Archaeology of Western Iran. Smithsonian Institution Press.

Holdaway, S., Phillipps, R., Emmitt, J., Wendrich, W., 2016. The Fayum revisited: reconsidering the role of the Neolithic package, Fayum north shore, Egypt. Quaternary International in press.

Horwitz, L.K., Tchernov, E., Ducos, P., et al., 1999. Animal domestication in the southern Levant. Paléorient 25 (2), 63–80.

Hunt, H.V., Campana, M.G., Lawes, C., et al., 2011. Genetic diversity and phylogeography of broomcorn millet (*Panicum miliaceum* L.) across Eurasia. Molecular Ecology 20, 4756–4771.

Jepma, M., Verdonschot, R.G., van Steenberger, H., et al., 2012. Neural mechanisms underlying the induction of relief of perceptual curiosity. Frontiers in Behavioral Neuroscience 6 (5), 1–9. http://dx.doi.org/10.3389/fnbeh.2012.00005.

Jones, M., Brown, T., 2007. Selection, cultivation and reproductive isolation: a reconsideration of the morphological and molecular signals of domestication. In: Denham, T., Iriarte, J., Vrydaghs, L. (Eds.), Rethinking Agriculture: Archaeological and Ethnoarchaeological Perspectives. Left Coast Press, Walnut Creek, CA, pp. 36–49.

Jones, G., Jones, H., Charles, M.P., et al., 2012. Phylogeographic analysis of barley DNA as evidence for the spread of Neolithic agriculture through Europe. Journal of Archaeological Science 39, 3230–3238.

Jones, E.R., Gonzalez-Fortes, G., Connell, S., et al., 2015. Upper Palaeolithic genomes reveal deep roots of modern Eurasians. Nature Communications. http://dx.doi.org/10.1038/ncomms9912.

Jones, R., Meehan, B., 1989. Plant foods of the Gidjinggali: ethnographic and archaeological perspectives from northern Australia on tuber and seed exploitation. In: Harris, D.R., Hillman, G.C. (Eds.), Foraging and Farming: Evolution of Plant Exploitation. Unwin Hyman, London, pp. 120–135.

Jórdeczka, M., Królik, H., Masojć, M., Schild, R., 2013. Hunter–gatherer cattle-keepers of early Neolithic el Adam type from Nabta playa: latest discoveries from site E–06–1. African Archaeological Review 30, 253–284. http://dx.doi.org/10.1007/s10437-013-9136-1.

Kahneman, D., 2003. Maps of bounded rationality: psychology for behavioral economics. American Economic Review 93, 1449–1475.

Kelly, R.L., 2013. The Lifeways of Hunter-Gatherers: The Foraging Spectrum. Cambridge University Press, Cambridge.

Kimura, B., Marshall, F.B., Chen, S., et al., 2011. Ancient DNA from Nubian and Somali wild ass provides insights into donkey ancestry and domestication. Proceedings of the Royal Society B 278, 50–57. http://dx.doi.org/10.1098/rspb.2010.0708.

Kistler, L., Montenegro, A., Smith, B.D., et al., 2014. Transoceanic drift and the domestication of African bottle gourds in the Americas. Proceedings of the National Academy of Sciences of the United States of America 11, 2937–2941.

Kislev, M.E., Hartman, A., 2012. Food crops from Nahal Zehora. In: Gopher, A. (Ed.), Village Communities of the Pottery Neolithic Period in Menashe Hills, Israel: Archaeological Investigations at the Site of Nahal Zehora. Tel Aviv University, Tel-Aviv, pp. 1321–1325.

Kuijt, I., Finlayson, B., 2009. Evidence for food storage and predomestication granaries 11,000 years ago in the Jordan Valley. Proceedings of the National Academy of Sciences of the United States of America 106, 10966–10970.

Larson, G., Liu, R., Zhao, X., et al., 2010. Patterns of East Asian pig domestication, migration, and turnover revealed by modern and ancient DNA. Proceedings of the National Academy of Sciences of the United States of America 107, 7686–7691.

Larson, G., Karlsson, E.K., Angela Perri, A., et al., 2012. Rethinking dog domestication by integrating genetics, archeology, and biogeography. Proceedings of the National Academy of Sciences of the United States of America 109, 8878–8883.

Larson, G., Albarella, U., Dobney, K., Rowley-Conwy, P., et al., 2007. Ancient DNA, pig domestication, and the spread of the Neolithic into Europe. Proceedings of the National Academy of Sciences of the United States of America 104, 15276–15281.

Lavallé, D., 1995. The First South Americans. University of Utah Press, Salt Lake City.

Lee, G.-A., 2011. The transition from foraging to farming in prehistoric Korea. Current Anthropology 52, S307–S329.

Lee, G.-A., 2012. Archaeological perspectives on the origins of azuki (*Vigna angularis*). Holocene 23 (3), 453–459.

Lee, G.-A., Crawford, G.W., Liu, L., Chen, X., 2007. Plants and people from the early Neolithic to Shang periods in north China. Proceedings of the National Academy of Sciences of the United States of America 104, 1087–1092.

Lee, R.B., DeVore, I. (Eds.), 1968. Man the Hunter. Aldine Publishing Company, Chicago.

Lev, E., Kislev, M.E., Bar-Yosef, O., 2005. Mosuterian vegetal food in Kebara cave, Mt Carmel. Journal of Archaeological Science 32, 475–484.

Lev-Yadun, S., Gopher, A., Abbo, S., 2000. The cradle of agriculture. Science 288, 1602–1603.

Lindblad-Toh, K., Wade, C.M., Mikkelsen, T.S., et al., 2005. Genome sequence, comparative analysis and haplotype structure of the domestic dog. Nature 438, 803–819. http://dx.doi.org/10.1038/nature04338.

Linstädter, J., Medved, I., Solich, M., Weniger, G.-C., 2012. Neolithisation process within the Alboran territory: models and possible African impact. Quaternary International 274, 219–232.

Lipson, M., Po-Ru Loh, P.-R., Nick Patterson, N., et al., 2014. Reconstructing Austronesian population history in island southeast Asia. Nature Communications 5, 4689. http://dx.doi.org/10.1038/ncomms5689.

Litt, T., Ohlwein, C., Neumann, et al., 2012. Holocene climate variability in the Levant from the Dead Sea pollen record. Quaternary Science Reviews 49, 95–105.

Liu, G., 2007. Analysis of the sites. In: Yang, H., Liu, G., Tang, C. (Eds.), The Origin of Jades in East Asia; Jades of the Xinglongwa Culture. The Chinese University of Hong Kong, pp. 2–55.

Liu, l, 2015. A long process towards agriculture in the middle yellow river valley, china: evidence from macro- and micro-botanical remains. Journal of Indo-Pacific Archaeology 35, 3–14.

Liu, L., Field, J., Fullagar, R., Bestel, S., et al., 2010. What did grinding stones grind? New light on Early Neolithic subsistence economy in the Middle Yellow River Valley, China. Antiquity 84, 816–833.

Liu, L., Bestel, S., Shi, J., et al., 2013. Paleolithic human exploitation of plant foods during the last glacial maximum in North China. Proceedings of the National Academy of Sciences of the United States of America 110, 5380–5385.

Liu, L., Ge, W., Bestel, S., Jones, D., et al., 2011. Plant exploitation of the last foragers at Shizitan in the Middle Yellow River Valley China: evidence from grinding stones. Journal of Archaeological Science 38, 3524–3532.

Lu, T.L.-D., 1998. The microblade tradition in China: regional chronologies and significance in the transition to Neolithic. Asian Perspectives 37, 84–112.

Lu, T.L.-D., 1999. The Transition from Foraging to Farming and the Origin of Agriculture in China. BAR International Series.

Lu, H., Zhang, J., Liu, et al., 2009. Earliest domestication of common millet (*Panicum miliaceum*) in East Asia extended to 10,000 years ago. Proceedings of the National Academy of Sciences of the United States of America 106, 7367–7372.

Lubock, J., 1865. Pre-historic Times. Willams and Norgate, London.

Lukacs, J.R., 2002. Hunting and gathering strategies in prehistoric India: a biocultural perspective on trade and subsistence. In: Morrison, K.D., Junker, L.L. (Eds.), Forager-traders in South and Southeast Asia. Cambridge University Press, Cambridge, pp. 41–61.

Madella, M., Jones, M.K., Goldberg, P., et al., 2002. The exploitation of plant resources by Neanderthals in Amud Cave (Israel): the evidence from phytolith studies. Journal of Archaeological Science 29, 703–719.

Maher, L., Richter, T., Macdonald, D., et al., 2012. Twenty thousand-year-old huts at hunter-gatherers settlement in Eastern Jordan. PLoS One 7, e31447.

Mariotti Lippia, M., Foggia, B., Arangurenb, B., et al., 2015. Multistep food plant processing at Grotta Paglicci (Southern Italy) around 32,600 cal B.P. Proceedings of the National Academy of Sciences of the United States of America 112, 12075–12080.

Marshall, F.B., Dobney, K., Denham, T., Capriles, J.M., 2014. Evaluating the roles of directed breeding and gene flow in animal domestication. Proceedings of the National Academy of Sciences of the United States of America 111, 6153–6158.

Marshall, F., Weissbrod, L., 2011. Domestication processes and morphological change: through the lens of the donkey and African pastoralism. Current Anthropology 52, S397–S413.

Martin, L., Edwards, Y., 2013. Diverse strategies: evaluating the appearance and spread of domestic caprines in the southern Levant. In: Colledge, S., Conolly, J., Dobney, K., et al. (Eds.), The Origins and Spread of Domestic Animals in Southwest Asia and Europe. Left Coast Press, Walnut Creek, CA, pp. 49–82.

Mathias, P., Davis, J.A. (Eds.), 1989. The First Industrial Revolution. Balckwell, Oxford & Cambridge.

McGovern, P., 2003. Ancient Wine: The Search for the Origins of Viniculture. Princeton University Press, Princeton.

McMichael, C.H., Piperno, D.R., Bush, M.B., et al., 2012. Sparse pre-Columbian human habitation in western Amazonia. Science 336, 1429–1431.

Meadow, R.H., 1996. The origins and spread of agriculture and pastoralism in northwestern South Asia. In: Harris, D.R. (Ed.), The Origins and Spread of Agriculture and Pastoralism in Eurasia. Smithsonian Institution Press, pp. 390–412.

Mokyr, J., 2002. The Gifts of Athena: Historical Origins of the Knowledge Economy. Princeton University Press, Princeton.

Moore, J.D., 2014. A Prehistory of South America: Ancient Cultural Diversity on the Least Known Continent. University Press of Colorado, Boulder.

Morales, J., Pérez-Jordà, G., Peña-Chocarro, L., et al., 2013. The origins of agriculture in north-West Africa: macro-botanical remains from Epipalaeolithic and early Neolithic levels of Ifri Oudadane (Morocco). Journal of Archaeological Science 40, 2659–2669.

Moseley, M., 1997. The Incas and Their Ancestors: The Archaeology of Peru. Thames and Hudson, London.

Munro, N.D., 2004. Zooarchaeological measures of hunting pressure and occupation intensity in the Natufian. Current Anthropology 45, S5–S33.

Nadel, D., Weiss, E., Simchoni, O., et al., 2004. Stone age hut in Israel yields world's oldest evidence of bedding. Proceedings of the National Academy of Sciences of the United States of America 101, 6821–6826.

Naderia, S., Rezaeia, H.-R., Pompanona, F., et al., 2008. The goat domestication process inferred from large-scale mitochondrial DNA analysis of wild and domestic individuals. Proceedings of the National Academy of Sciences of the United States of America 105, 17659–17664.

Namdar, D., Amrani, A., Getzov, Milevski, I., 2014. Olive oil storage during the fifth and sixth millennia BC at Ein Zippori, Northern Israel. Israel Journal of Plant Sciences 1–14. http://dx.doi.org/10.1080/07929978.2014.960733.

Negi, C.S., 2010. The institution of taboo and the local resource management and conservation surrounding sacred natural sites in Uttarakhand, Central Himalaya. International Journal of Biodiversity and Conservation 2, 186–195.

Noshiro, S., Sasaki, Y., 2014. Pre-agricultural management of plant resources during the Jomon period in Japanda sophisticated subsistence system on plant resources. Journal of Archaeological Science 42, 93–106.

Oas, S.E., D"Andrea, A.C., Watson, D.J., 2015. 10,000 year history of plant use at Bosumpra Cave, Ghana. Vegetation History and Archaeobotany 24, 635–653. http://dx.doi.org/10.1007/s00334-015-0514-2.

Oota, H.,B., Pakendorf, G., Weiss, A., et al., 2005. Recent origin and cultural reversion of a hunter-Gatherer group. PLoS Biology 3, 536–542.

Orland, I.J., Bar-Matthews, M., Ayalon, A., et al., 2012. Seasonal resolution of eastern Mediterranean climate since 34 ka from Soreq cave speleothem. Geochimica et Cosmochimica Acta 89, 240–255.

Ottoni, C., Flink, L.G., Evin, A., et al., 2013. Pig domestication and human-mediated dispersal in western Eurasia revealed through ancient DNA and geometric morphometrics. Molecular Biology and Evolution 30, 824–832.

Ozkan, H., Willcox, G., Graner, A., et al., 2011. Geographic distribution and domestication of wild emmer wheat (*Triticum dicoccoides*). Genetic Resources and Crop Evolution 58 (1), 11–53 on line July 2010.

Özdoğan, M., 2011. Archaeological evidence on the westward expansion of farming communities from Eastern Anatolia to the Aegean and the Balkans. Current Anthropology 52, S415–S430.

Peleg, Z., Fahima, Z., Korol, A.B., et al., 2011. Genetic analysis of wheat domestication and evolution under domestication. Journal of Experimental Botany 62, 5051–5061, 2011.

Peters, J., Helmer, D., Von Den Deisch, A., Saña Segui, M., 1999. Early animal husbandry in the northern Levant. Paléorient 25 (2), 27–48.

Pinhasi, R., Fort, J., Ammerman, A.,J., 2005. Tracing the origin and spread of agriculture in Europe. PLoS Biology 3 (12), 2020–2028. http://dx.doi.org/10.1371/journal.pbio.0030410.

Pinhasi, R., Thomas, M.G., Hofreiter, M., et al., 2012. The genetic history of Europeans. Trends in Genetics 28 (10), 496–505.

Piperno, D.R., 2011. The origins of plant cultivation and domestication in the new world tropics: patterns, process, and new developments. Current Anthropology 52 (S4), S453–S470.

Piperno, D.R., Dillehay, T.D., 2008. Starch grains on human teeth reveal early broad crop diet in northern Peru. Proceedings of the National Academy of Sciences of the United States of America 105, 19622–19627.

Piperno, D.R., Pearsall, D.M., 1998. The Origins of Agriculture in the Lowland Neotropics. Academic Press, New York.

Piperno, D.R., Ranere, A.J., Holstb, I., et al., 2009. Starch grain and phytolith evidence for early ninth millennium B.P. maize from the Central Balsas River Valley, Mexico. Proceedings of the National Academy of Sciences of the United States of America 106, 5019–5024.

Piperno, D.R., Smith, B.D., 2012. The origins of food production in Mesoamerica. In: Nichols, D.L., Pool, C.A. (Eds.), The Oxford Handbook of Mesoamerican Archaeology. Oxford University Press, New York, pp. 151–164.

Piperno, D.R., Weiss, E., Holst, I., Nadel, D., 2004. Processing of wild cereal grains in the upper Palaeolithic revealed by starch grain analysis. Nature 430, 670–673.

Piperno, D.R., Holst, I., Winter, I., McMillan, O., 2015. Teosinte before domestication: experimental study of growth and phenotypic variability in Late Pleistocene and early Holocene environments. Quaternary International 363, 65–77.

Price, T.D., Fienman, G. (Eds.), 2010. Pathways to Power: New Perspectives on the Origins of Social Inequality. Springer.

Pujol, B., Gigot, G., Laurent, G., et al., 2002. Germination ecology of cassava (*manihot esculenta* crantz, Euphorbiaceae) in traditional agroecosystems: seed and seedling biology of a vegetatively propagated domesticated plant. Economic Botany 56, 366–379.

Purugganan, M.D., Fuller, D.Q., 2009. The nature of selection during plant domestication. Nature 457, 843–848.

Purugganan, M.D., Fuller, d.q, 2011. Archaeological data reveal slow rates of evolution during plant domestication. Evolution 65 (1), 171–183. http://dx.doi.org/10.1111/j.1558-5646.2010.01093.x.

Quilter, J., 2014. The Ancient Central Andes. Routlege, London & New York.

Ranere, A.J., Piperno, D.R., Holst, I., et al., 2009. The cultural and chronological context of early Holocene maize and squash domestication in the Central Balsas River Valley, Mexico. Proceedings of the National Academy of Sciences of the United States of America 106, 5014–5018.

Redding, R.W., 2005. Breaking the mold: a consideration of variation in the evolution of animals domestication. In: Vigne, J.D., Peters, J., Helmer, D. (Eds.), First Steps of Animal Domestication. Oxbow Books, Oxford, pp. 41–48.

Ridout-Sharpe, J., 2015. Changing lifestyles in the northern Levant: late Epipalaeolithic and early Neolithic shells from Tell Abu Hureyra. Quaternary International 390, 102–116.

Riehl, S., Benz, M., Conard, N.J., et al., 2011. Plant use in three Pre-Pottery Neolithic sites of the northern and eastern Fertile Crescent: a preliminary report. Vegetation History and Archaeobotany 21, 95–106.

Riehl, S., Zeidi, M., Conard, N.J., 2013. Emergence of agriculture in the foothills of the Zagros mountains of Iran. Science 341, 65–67.

Richerson, P.J., Boyd, R., Bettinger, R.L., 2001. Was agriculture impossible during the Pleistocene but mandatory during the Holocene? A climate change hypothesis. American Antiquity 66, 387–411.

Rosen, A.M., 2010. Natufian plant exploitation: management risk and stability in an environment of change. Eurasian Prehistory 7, 117–131.

Rosenberg, M., Redding, R.W., 2000. Hallan Çemi and early village organization in eastern Anatolia. In: Kuijt, I. (Ed.), Life in Neolithic Farming Communities: Social Organization, Identity, and Differentiation. Plenum Press, New York, pp. 39–61.

Roullier, C., Benoit, L., McKey, D.B., Lebot, V., 2013. Historical collections reveal patterns of diffusion of sweet potato in Oceania obscured by modern plant movements and recombination. Proceedings of the National Academy of Sciences of the United States of America 110, 2205–2210.

Rowley-Conwy, P., 2011. Westward Ho! The spread of agriculturalism from central Europe to the Atlantic. Current Anthropology 52 (S4), 431–451.

Romero, I.G., Mallick, C.B., Liebert, A., et al., 2011. Herders of Indian and European cattle share their predominant Allele for lactase persistence. Molecular Biology and Evolution. http://dx.doi.org/10.1093/molbev/msr190A.

Salque, M., Bogucki, P.I., Pyze, J., et al., 2013. Earliest evidence for cheese making in the sixth millennium BC in northern Europe. Nature 493, 522–525.

Schoch, W.H., Bigga, G., Böhner, U., et al., 2015. New insights on the wooden weapons from the Paleolithic site of Schöningen. Journal of Human Evolution 89, 214–225.

Schmidt, K., 2005. "Ritual Centers" and the Neolithisation of Upper Mesopotamia. Neo-Lithics 2 (05), 13–21.

Schmidt, K., 2011. Göbekli Tepe. In: Özdoğan, M., Basgelen, N., Kuniholm, P. (Eds.), The Neolithic of Turkey: The Euphrates basin. Archaeology and Art Publications, Istanbul, pp. 41–83.

Shennan, S., 2000. Population, culture history, and the dynamics of culture change. Current Anthropology 41, 811–835.

Shelach, G., 2000. The earliest Neolithic cultures of northeast China: Recent discoveries and new perspectives on the beginning of agriculture. Journal of World Prehistory 14, 363–413.

Sherratt, A., 1981. Plough and pastoralism: aspects of the secondary products revolution. In: Hodder, I., Isaac, G., Hammond, N. (Eds.), Pattern of the Past: Studies in Honor of David Clarke. Cambridge University Press, Cambridge, pp. 261–306.

Savolainen, P., Zhang, Y.P., Luo, J., et al., 2002. Genetic evidence for an East Asian origin of domestic dogs. Science 298, 1610–1613.

Sauer, C.O., 1952. Agricultural Origins and Dispersals. MIT Press, Cambridge.

Simmons, A.H., 2007. The Neolithic Revolution in the Near East. Transforming the Human Landscape. The University of Arizona Press.

Skoglund, P., Ersmark, E., Palkopoulou, E., Dalén, L., 2015. Ancient wolf genome reveals an early divergence of domestic dog ancestors and admixture into high-latitude breeds. Current Biology 11, 1515–1519.

Smith, B.D., 2011. The cultural context of plant domestication in Eastern North America. Current Anthropology 52, S471–S484.

Snir, A., Nadel, D., Groman-Yaroslavski, I., et al., 2015. The origins of cultivation and proto-weeds, long before Neolithic farming. PLoS One 1–22. http://dx.doi.org/10.1371/journal.pone.0131422.

Speth, J.D., 2010. The Paleoanthropology and Archaeology of Big-game Hunting: Protein, Fat, or Politics? Springer, New York.

Speller, C.F., Kemp, B.M., Wyatt, S.D., et al., 2009. Ancient mitochondrial DNA analysis reveals complexity of indigenous North American turkey domestication. Proceedings of the National Academy of Sciences of the United States of America 107, 2807–2812.

Spooner, D.M., McLean, K., Ramsay, G., et al., 2005. A single domestication for potato based on multilocus amplified fragment length polymorphism genotype. Proceedings of the National Academy of Sciences of the United States of America 102, 14694–14699.

Stock, F., Gifford-Gonzalez, D., 2013. Genetics and African cattle domestication. African Archaeological Review 30, 51–72. http://dx.doi.org/10.1007/s10437-013-9131-6.

Starkovich, B.M., Stiner, M.C., 2009. Hallan Çemi Tepesi: high-ranked game exploitation alongside intensive seed processing at the epipaleolithic-Neolithic transition in southeastern Turkey. Anthropozoologica 44, 41–61.

Stevens, N.E.S., McElreath, R., 2015. When are two tools better than one? Mortars, milling slabs and the California acorn economy. Journal of Anthropological Archaeology 37, 100–111.

Tanno, K., Willcox, G., 2006. How fast was wild wheat domesticated? Science 311, 1886.

Tanno, K.-I., Willcox, G., 2012. Distinguishing wild and domestic wheat and barley spikelets from early Holocene sites in the Near East. Vegetation History and Archaeobotany 21, 107–115.

Tanno, K.-I., Willcox, G., Muhesen, S., et al., 2013. Preliminary results from analysis of charred plant remains from a burnt Natufian building at Dederiyeh cave in northwest Syria. In: Bar-Yosef, O., Valla, F. (Eds.), Natufian Foragers in the Levant: Terminal Pleistocene Changes in Western Asia. IMP Ann-Arbor, Michigan, pp. 83–87.

Taylor, R.E., Bar-Yosef, O., 2014. Radiocarbon Dating: An Archaeological Perspective. Left Coast Press, Walnut Creek, CA.

Tchernov, E., 1991. Biological evidence for human sedentism in southwest Asia during the Natufian. In: Bar-Yosef, O., Valla, F.R. (Eds.), The Natufian Culture in the Levant. International Monographs in Prehistory, Ann Arbor, pp. 315–340.

Tchernov, E., Valla, F.R., 1997. Two new dogs, and other Natufian dogs, from the southern Levant. Journal of Archaeological Science 24, 65–95.

Thieme, H., 1997. Lower Paleolithic hunting spears from Germany. Nature 385, 807–810.

Thomas, W.L., 1955. Man's Role in Changing the Face of the Earth. University of Chicago Press.

Torfstein, A., Goldstein, S.L., Stein, M., Enzel, Y., 2013. Impacts of abrupt climate changes in the Levant from last glacial dead sea levels. Quaternary Science Reviews 69, 1–7.

Tresset, A., Bollongino, R., Edwards, C.J., et al., 2009. Early diffusion of domestic bovids in Europe: an indicator for human contacts, exchange and migrations? In: D'Errico, F., Hombert, J.-M. (Eds.), Becoming Eloquent: Advances in the Emergence of Human Language, Human Cognition and Modern Cultures. John Benjamins Publishing Company, pp. 69–90.

Trut, L., Oskina, I., Kharlamova, A., et al., 2009. Animal evolution during domestication: the domesticated fox as a model. BioEssays 31, 349–360. http://dx.doi.org/10.1002/bies.200800070.

Ungar, P.S. (Ed.), 2007. The Evolution of the Human Diet: The Known, the Unknown, and the Unknowable. Oxford University Press.

Valla, F.R., 1988. Aspect du sol dl'abri 131 de Mallaha (Eynan). Paléorient 15, 283–296.

Vavilov, N., 1926. Studies on the Origins of Cultivated Plants. Nst. Appl. Bot. Plant Breed, Leningrad.

Veeramah, K.R., Novembre, J., 2014. Demographic events and evolutionary forces shaping European genetic diversity. Cold Spring Harbor Perspectives in Biology 6. http://dx.doi.org/10.1101/cshperspect.a008516.

Vigne, J.-D., 2011. The origins of animal domestication and husbandry: a major change in the history of humanity and the biosphere. Comptes Rendus Biologies 334, 171–181.

Vigne, J.-D., 2013. Domestication process and domestic ungulates: new observations from Cyprus. In: Colledge, S., Conolly, J., Dobney, K., Manning, K., Shennan, S. (Eds.), The Origins and Spread of Domestic Animals in Southwest Asia and Europe. Left Coast Press, Walnut Creek, CA, pp. 115–128.

Vigne, J.D., 2015. Early domestication and farming: what should we know or do for a better understanding? Anthropozoologica 50 (2), 123–150.

Vigne, J.-D., Coucchi, T., 2005. Premières navigations au Proche-Orient: les informations indirectes de Chypre. Paléorient 31, 186–194.

Vigne, J.-D., Carrère, I., Briois, F., Guilaine, J., 2011. The early process of mammal domestication in the Near East: new evidence from the pre-Neolithic and pre-pottery Neolithic in Cyprus. Current Anthropology 52, S255–S271.

Vigne, J.-D., Briois, F., Zazzo, A., Willcox, G., et al., 2012. First wave of cultivators spread to Cyprus at least by 10,600 y ago. Proceedings of the National Academy of Sciences of the United States of America 109, 8445–8449.

Waguespack, N.M., 2005. What do women do in large-game hunting societies? The organization of male and female labor in foraging societies: implications for early Paleoindian archaeology. American Anthropological 107, 666–676.

Wayne, R.K., vonHoldt, B.M., 2012. Evolutionary genomics of dog domestication. Mammalian Genome 23, 3–18.

Weiss, E., 2015. "Beginnings of fruit growing in the old world" – two generations later. Israel Journal of Plant Sciences 62, 75–85.

Weiss, E., Kislev, M.E., Hartmann, A., 2006. Autonomous cultivation before domestication. Science 312, 1608–1610.

Weiss, E., Wetterstrom, W., Nadel, D., Bar-Yosef, O., 2004. The broad spectrum revisited: evidence from plant remains. Proceedings of the National Academy of Sciences of the United States of America 101, 9551–9555.

Weninger, B., Clare, L., Rohling, E.J., et al., 2009. The impact of rapid climate change on prehistoric societies during the Holocene in the eastern Mediterranean. Documenta Praehistorica 36, 551–583.

Wetterstrom, W., 1993. Foraging and farming in Egypt: the transition from hunting and gathering to horticulture in the Nile valley. In: Shaw, T., Sinclair, P., Andah, B., Okpoko, A. (Eds.), The Archaeology of Africa: Food, Metals and Towns. Routledge, pp. 165–226.

Wetterstrom, W., 1998. The origins of agriculture in Africa: with particular reference to sorghum and pearl millet. The Review of Archaeology 19, 30–47.

Wengrov, D., Dee, M., Foster, S., et al., 2014. Cultural convergence in the Neolithic of the Nile Valley: a prehistoric perspective on Egypt's place in Africa. Antiquity 88, 95–111.

Willcox, G., 2005. The distribution, natural habitats and availability of wild cereals in relation to their domestication in the Near East: multiple events, multiple centres. Vegetation History and Archaeobotany 14, 534–541.

Willcox, G., 2012. Searching for the origins of arable weeds in the Near East. Vegetation History and Archaeobotany 21, 163–167.

Willcox, G., 2012b. Pre-domestic cultivationduring the late Pleistocene and early Holocene in the northern Levant. In: Gepts, P., Famula, T.R., Bettinger, et al. (Eds.), Biodiversity in Agriculture. Cambridge University Press, pp. 92–109.

Willcox, G., Nesbitt, M., Bittmann, F., 2012. From collecting to cultivation: transitions to a production economy in the Near East. Vegetation History and Archaeobotany 21, 81–83.

Willcox, G., Stordeur, D., 2012. Large-scale cereal processing before domestication during the tenth millennium BC cal. in northern Syria. Antiquity 86, 99–114.

Willcox, G., Savard, M., 2011. Botanical evidence for the adoption of cultivation in Southeast Turkey. In: Ozdogan, M., Basgelen, N., Kuniholm, P. (Eds.), The Neolithic in Turkey: The Tigris Basin. Archaeology and Art Publications, Istanbul, pp. 267–280.

Wu, X., Zhang, C., Goldberg, P., et al., 2012. Early pottery et 20,000 years ago in Xianrendong, China. Science 336, 1696–1700.

Wrangham, R., Conklin-Brittain, N.L., Hunt, K.D., 1998. Dietary response of chimpanzees and Cercopithecines to seasonal variation in fruit abundance. I. Antifidants. International Journal of Primatology 19 (6), 949–970.

Yang, X., Wan, Z., Perry, L., et al., 2012. Early millet use in northern China. Proceedings of the National Academy of Sciences of the United States of America 109, 3726–3730.

Yang, X., Barton, H.J., Wan, Z., et al., 2013. Sago-type palms were an important plant food prior to rice in southern subtropical China. PLoS One 8 (5), e63148. http://dx.doi.org/10.1371/journal.pone.0063148.

Yang, X., Fuller, D.Q., Huan, X., et al., 2015. Barnyard grasses were processed with rice around 10,000 years ago. Nature Scientific Reports 5, 16251. http://dx.doi.org/10.1038/srep16251.

Yaroshevich, A., Kaufman, D., Nuzhnyy, D., et al., 2010. Designs of microlithic projectiles during the Late Epi-Palaeolithic in the Southern Levant tested by archery experiments. Journal of Archaeological Science 37, 368–388.

Yen, D.E., 1989. The domestication of environment. In: Harris, D.R., Hillman, G.C. (Eds.), Foraging and Farming: The Evolution of Plant Exploitation. Unwin Hyman, London, pp. 55–75.

Yuan, J., Flad, R.K., 2002. Pig domestication in ancient China. Antiquity 76, 724–732.

Zeder, M.A., 2011. The origins of agriculture in the Near East. Current Anthropology 52, S221–S235.

Zeder, M., 2012. Domestication of animals. Journal of Archaeological Research 68 (2), 161–190.

Zeder, M., 2015. Core questions in domestication research. Proceedings of the National Academy of Sciences of the United States of America 112, 3191–3198.

Zhang, C., Hung, H.-C., 2012. Later hunter-gatherers in southern China, 18 000–3000 BC. Antiquity 86, 11–29.

Zhang, C., Hung, H-c, 2013. Jiahu 1: earliest farmers beyond the Yangtze river. Antiquity 87, 46–63.

Zhao, Z., 2010. New data and new issues for the study of origins of rice agriculture in China. Archaeological and Anthropological Sciences 2, 99–105.

Zhao, Z., 2011. New archaeobotanic data for the study of the origins of agriculture in China. Current Anthropology 52, S295–S306.

Zarrillo, S., Pearsall, D.M., Raymond, J.S., et al., 2008. Directly dated starch residues document early formative maize (*Zea mays* L.) in tropical Ecuador. Proceedings of the National Academy of Sciences of the United States of America 105, 5006–5011.

Zheng, Y.-F., Sun, G.-P., Chen, X.-G., 2007. Characteristics of the short rachillae of rice from archaeological sites dating to 7000 years ago. Chinese Science Bulletin 52, 1654–1660.

Zilhao, J., 2014. Early prehistoric navigation in the western Mediterranean: implications for the Neolithic transition in Iberia and the Maghreb. Eurasian Prehistory 11 (2), 185–200.

Zohary, D., Hopf, M., Weiss, E., 2012. Domestication of Plants in the Old World: The Origin and Spread of Cultivated Plants in Southwest Asia, Europe and the Mediterranean Basin. Oxford University Press, Oxford.

Chapter 20

The Quantum Origin of Life: How the Brain Evolved to *Feel Good*

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INTRODUCTION: WHICH CAME FIRST, FEELINGS OR THE BRAIN?

What Drives Conscious Behavior?

According to Darwin's theory of evolution, adaptations through random mutations serve an organism's genes, the fittest genes surviving through reproductive success. However, Darwin's theory renders consciousness epiphenomenal and illusory, leaves apparent gaps in evolution, and has been questioned as its sole guiding force. For example, Kauffman (1993) has invoked principles of self-organization and nonlinear emergence in life and its evolution. But to what end? What is life evolving toward? What's the point?

In psychology and cognitive neuroscience, purposeful conscious behavior is predicated on personal reward, on an animal or human wanting to feel good (or avoid feeling bad). Conscious feelings drive behavior, whether for immediate or delayed gratification, altruism ("it *feels* better to give than to receive"), and/or spiritual peace and contentment. Primacy of feelings has been asserted since Epicurus in ancient Greece, Freud's (1961) "pleasure principle" in psychiatry, and dopamine-mediated "reward" in psychology and neuroscience. Damasio (1999) has emphasized the primacy of emotional feelings, as has Panksepp (1998), and Peil (2014) who suggests they derive from a "deeper authority" which may regulate and guide our behaviors.

In philosophical terms, feelings and conscious awareness are composed of mental features termed qualia, whose essential nature remains a scientific mystery—what it is like to *be* (Nagel, 1974), also known as the hard problem (Chalmers, 1996). We could have been unfeeling zombies, programmed to promote our species, but without qualia and inner experience. But we *do* have them, and we *are* conscious, although how and why remain unknown.

The mainstream view in neuroscience contends consciousness, feelings and qualia emerge from complex computation among many simple brain neurons (Dennett, 1991; Tononi, 2012; Churchland, 2013). Such computational emergence—brain-as-computer—implies consciousness appeared on earth as an adaptation of biological evolution, and may eventually be replicated in silicon. However, these views neglect the question of what *life* is; are based on cartoon-like abstractions of actual neurons; and fail to provide testable predictions, falsifiability, nor any semblance of experimental validation.

These failings have pushed some computationalists toward philosophical panpsychism, the assertion that qualia are properties of matter (Koch, 2012), or of discrete events in an experiential medium (panexperientialism, as proposed by Whitehead, 1929, 1933). Others suggest mental qualities derive from deeper, intrinsic features of the universe, features giving *rise* to qualia, along with matter, charge, spin, and various cosmological parameters (Penrose, 1989; Chalmers, 1996). In these views, qualia-like features preceded life, perhaps encoded in reality, in the structure, or makeup of the universe described as fundamental spacetime geometry. If so, pleasurable qualia may have preceded life, and prompted its origin and evolution to optimize feelings.

However in looking inward in search of qualia, panpsychists and panexperientialists must encounter the mysterious world of quantum mechanics, and specifically the "measurement problem," related to the "collapse of the wave function." At small scales, and the cutoff is seemingly variable, strange laws of quantum physics reign, eg, quantum particles exist in superposition of multiple states or locations simultaneously, described by a quantum wave function. Such superpositions are not seen in our everyday world, as efforts to measure or observe them apparently

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00020-X

result in collapse to definite states. Why quantum superpositions are not seen is a mystery known as the measurement problem, which seems in some way related to consciousness.

Experiments from the early 20th century appeared to show that conscious observation caused superposition wave functions to collapse to definite states, randomly choosing a particular reality. Consciousness was said to collapse the wave function (attributed to von Neumann, Wigner, Stapp, and Chalmers—see Stapp, 2007—but often termed the Copenhagen interpretation, after the Danish origin of Niels Bohr; see below). The Copenhagen interpretation allowed useful quantum experiments, but placed consciousness outside science, as an extrinsic entity causing collapse. Other interpretations include multiple worlds (Everett, 1957), in which each superposition possibility branches and evolves to form its own universe, resulting in an infinite number of parallel worlds.

Still others stipulate various objective thresholds for quantum state reduction (objective reduction, or OR), one by Sir Roger Penrose (1989, 1994) combining features of the Copenhagen interpretation and multiple worlds, and introducing consciousness into science as an intrinsic feature of the universe. To do so, Penrose characterized superpositions as in the first step in multiple worlds, separations in spacetime geometry, and the structure of the universe. But unlike multiple worlds, spacetime separations, according to Penrose, are unstable, separations continuing only until reaching an objective threshold related to the quantum uncertainty principle, $E_G = h/t$. The magnitude of the superposition is E_G (its gravitational self-energy), h is the Planck–Dirac constant and t the time at which OR self-collapse occurs.

In this approach, whenever superpositions reach threshold, OR events select particular classical states, accompanied by moments of (proto) conscious experience—qualia, basic units of feeling and awareness. The choice of classical states in OR events are influenced by (resonate with) what Penrose termed Platonic values embedded in the fine scale structure of the universe. The qualitative feeling of each quale, ie, good, bad, or otherwise, would depend on resonance and geometry of specific spacetime separations with deeper, Platonic levels of the universe. Most significantly, unlike the Copenhagen interpretation in which consciousness causes collapse, Penrose OR proposes that collapse *causes* consciousness (or that collapse *is* consciousness).

In this regard, Penrose OR is aligned with the process philosophy of Alfred North Whitehead (1929, 1933) who viewed consciousness as a sequence of discrete "occasions of experience." Abner Shimony (1993) suggested Whitehead conscious events, or 'occasions' were equivalent to quantum state reductions, or moments of collapse of the wave function. Generally, Whitehead occasions are "simple, dull and monotonous," and must be "combined," or "organized" into full, rich conscious moments. Similarly, noncognitive, protoconscious qualia occurring with each OR event must be combined, organized, or orchestrated into full rich conscious experience, as described in an iconoclastic theory, orchestrated objective reduction (Orch OR), put forth in the mid-1990s by Sir Roger Penrose and this author (Penrose and Hameroff, 1995; Hameroff and Penrose, 1996a,b, 2014a–c).

Orch OR suggests that conscious awareness and intentional purpose derive from organized (orchestrated) OR events in cytoskeletal structures called microtubules inside brain neurons. Microtubules are self-assembling lattice polymers of the protein tubulin which organize intracellular activities, process information, and vibrate coherently in various related frequencies over a wide spectrum, from terahertz through gigahertz, megahertz, and kilohertz (Sahu et al., 2013a,b, 2014). Orchestration implies that microtubule quantum states are organized through sensory inputs, memory and natural microtubule resonances prior to OR threshold to account for conscious cognition and full, rich conscious experience (Orch OR). Microtubule states selected in Orch OR events in neuronal dendrites and soma can regulate synaptic plasticity and trigger axonal firings to exert causal action and conscious behavior.

Protoconscious OR events occurring throughout the universe would be random and disjointed, metaphorically like isolated sounds and tones, eg, noise, of an orchestra warming up. On the contrary, sequences of Orch OR events would be akin to music, a symphony, jazz, Indian raga, or rock-and-roll classic. Such proposed Orch OR music, vibrations, and resonances in the fine-scale structure of the universe would be self-aware, not needing a listening audience.

However, the notion of functional quantum biology has been viewed skeptically. Technological quantum devices require extreme cold and isolation to avoid disruption by thermal decoherence, and so living systems have been considered too warm, wet, and noisy for functional quantum mechanisms. But plant photosynthesis uses quantum coherence in warm sunlight to produce chemical energy and food (Engel et al., 2007). Photons collected by plants are converted to electron resonance excitations (excitons), and transferred through a protein for conversion to chemical energy, propagating as quantum superposition of all possible pathways through a group of eight chromophores. These chromophores are comprised of nonpolar pi electron resonance clouds, geometrically arrayed nanometers apart, and coupled to coherent vibrations (see below). Buried in nonpolar, hydrophobic (water-aversive) regions, the chromophores constitute a quantum underground, shielded from decoherence, or premature OR via the polar, aqueous environment. Without quantum coherence, food would not be prevalent, and perhaps life could not exist at all.

Useful mechanisms are conserved in evolution. If a potato or asparagus can utilize quantum coherence, our brains, and specifically microtubules, might be expected to do so for cognition and consciousness.

The internal structure of microtubule protein subunits (tubulin) appears analogous to the quantum underground of pi resonance chromophores in plant photosynthesis. Computer models of tubulin structure show pi electron resonance clouds in aromatic amino acid rings of tryptophan, phenylalanine, and tyrosine in clusters and channels (Craddock et al., 2012a). Thus pi resonance regions in both photosynthesis proteins and tubulin in microtubules are buried and arrayed in a (dry) nonpolar solubility region shielded from (wet) polar interactions—a quantum underground. This particular solubility region is precisely where anesthetic gas molecules bind and selectively erase consciousness (the Meyer–Overton correlation—see below), and seems to be the origin of consciousness. Recent studies suggest anesthetics act by dampening terahertz (10^{12} Hz) quantum dipole oscillations in microtubule interiors (Pan et al., 2007; Emerson et al., 2013; Craddock et al., 2015), these rapid oscillations being the inner apex of a spatiotemporal hierarchy leading to electroencephalography (EEG; see Fig. 20.15).

According to Orch OR, quantum states and dipole oscillations in pi resonance clouds in a Meyer–Overton quantum underground within neuronal microtubules are orchestrated by synaptic inputs, memory, and vibrational resonance. This enables superpositions to avoid random, noncognitive interactions, and solely process purposeful and meaningful information. Thus when the $E_G = h/t$ threshold is met in orchestrated conditions, fully conscious Orch OR moments are said to occur, resonating with deeper level Platonic values in spacetime geometry. In pursuit of good feelings, Orch OR connects consciousness to the fine-scale structure of the universe. Over appropriate time scales, Orch OR events optimize pleasurable qualia.

On the biological side, Orch OR is fully consistent with known neuroscience, action of anesthetics and psychoactive drugs; generates testable predictions (some validated, none refuted); has medical and philosophical implications; provides mental states with causal power and intentional awareness; and surpasses other theories of consciousness in terms of evidence and testability. Similar to panpsychism, Orch OR implies that qualia, ie, feelings, preceded life.

It is suggested here that primitive protoconscious feelings occurred via Penrose OR in pi electron resonance clouds of micelle-like structures of dopamine-like molecules in nonpolar regions of the prebiotic primordial soup, the original quantum underground. OR-mediated feelings provided feedback and motivation for self-organizing pi resonance clouds (pi stacks) in the origin and evolution of life, and the brain. Intention and purpose optimized qualia. Life and the brain evolved to feel good.

CONSCIOUSNESS ON THE EDGE BETWEEN QUANTUM AND CLASSICAL WORLDS

In a broad sense, reality is described by two worlds: our familiar material (classical) world predictably follows the laws of Newton, Maxwell, and others. However, at small scales (and the size cutoff is unknown and seemingly variable), strange quantum laws reign. For example, quantum particles exist in multiple locations or states simultaneously, coexisting possibilities known as quantum superposition, represented by a quantum wave function. But we do not see quantum superpositions in our perceived world, reality somehow materializing from quantum possibilities, the wave function appearing to collapse to definite states. How and why this happens remain unknown, seemingly related to measurement and conscious observation, known as the measurement problem in quantum mechanics.

Another quantum feature is coherence, or condensation, in which quantum particles unify as single objects governed by one wave function, for example Bose-Einstein condensates. If any particle is perturbed, others feel it and react, prompting suggestions that quantum coherence supports binding and synchrony of mental and physiological events. A third quantum feature is nonlocal entanglement in which quantum particles remain connected when spatially separated, a bizarre prediction but conclusively demonstrated, and commonly utilized in quantum information technology. Entanglement may include temporal nonlocality, explaining backward time referral of subjective information in the brain, eg, Libet's et al. (1979) sensory experiments, enabling real time conscious control of our actions (Hameroff, 2012).

Why do not we see quantum superpositions in our consciously perceived world? This is the measurement problem, and interpretations include:

- The *conscious observer* (*Copenhagen interpretation*). Early quantum experiments seemed to indicate that if a machine measured a quantum system, the results remained in superposition until observed by a human. Proposed by Eugene Wigner, John von Neumann, and more recently Henry Stapp and David Chalmers, the conscious observer approach allowed Niels Bohr (whose Danish origin prompted the Copenhagen interpretation) and others to ignore questions related to the reality of superposition, and pragmatically perform quantum experiments.

  But the Copenhagen interpretation led to paradox. Erwin Schrödinger considered implications of an unobserved superposition amplified to macroscopic scale in his still-famous thought experiment known as Schrödinger's cat. Imagine a cat in a box with a vial of poison. Release of the poison is coupled to the state

of a quantum superposition. According to Copenhagen, Schrödinger noted, the cat would be both dead and alive until the box is opened and the cat observed by a conscious observer. Copenhagen associated consciousness with collapse, but cast it as a mysterious entity outside science.

- *Decoherence*. This approach suggests that any interaction of a quantum superposition with its classical environment, eg, by thermal interactions, degrades the quantum system. But decoherence does not address isolated superpositions, nor explain how quantum systems can ever be isolated. Moreover, some quantum processes are enhanced by environmental heat and/or noise.
- *Multiple worlds interpretation* (MWI; Everett, 1957). MWI claims each possibility in any superposition evolves without collapse, producing its own reality, resulting in an infinite number of parallel universes. Despite a lack of testability, MWI is extremely popular.
- *Objective reduction* (*OR*). These approaches suggest quantum superpositions evolve by the Schrödinger equation until reaching an objective threshold, at which collapse (reduction) occurs. Among these, Sir Roger Penrose (1989, 1994, 1996) described a specific OR threshold at which wave functions collapse, selecting classical states and producing quantized moments of protoconscious qualia.

Penrose began by addressing superposition—how particles can be in two or more places simultaneously—in terms of Einstein's general relativity in which matter is equivalent to spacetime curvature. That equivalence was famously verified at large scales (eg, distant starlight bending around the sun) by Sir Arthur Eddington in 1919, but Penrose applied it to microscopic scales, eg, tiny particles as tiny spacetime curvatures. Superpositions are then regions of alternate curvatures, separated spacetime (Fig. 20.1).

Spacetime separations would occur also in MWI, each curvature evolving its own universe (Fig. 20.2, left). But in Penrose OR, spacetime separations are unstable, and proposed to self-collapse, or undergo reduction by an objective

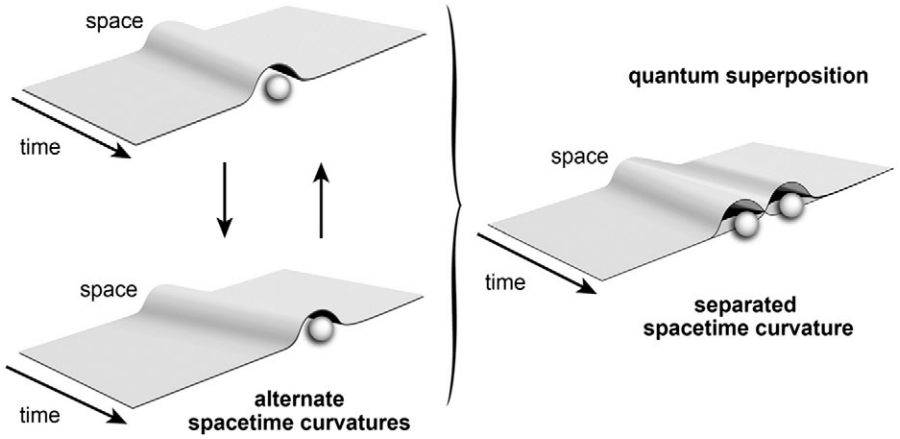

FIGURE 20.1 Spacetime geometry schematized as one spatial and one temporal dimension in which particle location is represented as curvature. (A) Top and bottom show spacetime histories of two alternative particle locations. (B) Quantum superposition of both particle locations as bifurcating spacetime depicted as the union (glued together version) of the two alternative histories. *Adapted from Penrose, R., 1989. The Emperor's New Mind: Concerning Computers, Minds, and the Laws of Physics. Oxford University Press, Oxford, p. 338.*

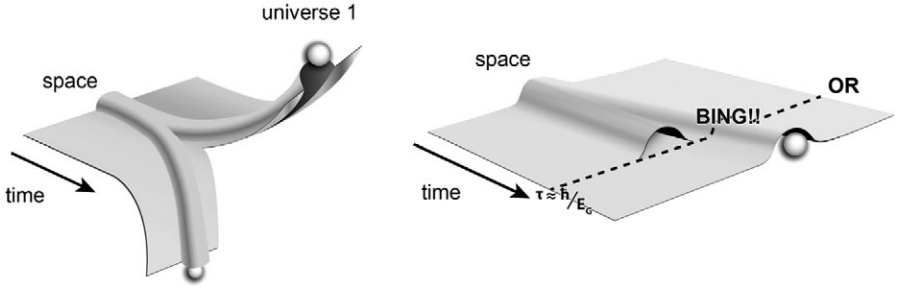

FIGURE 20.2 Two views of the fate of superpositions. Left: Each possibility evolves in its own universe, as per the multiple words interpretation (MWI). Right: Penrose objective reduction (OR); as superposition curvature E reaches threshold (by $E_G = \hbar/\tau$), OR occurs and one particle ceases to exist. The other location/curvature is selected, and becomes classical, accompanied by a moment of conscious experience (BING).

threshold given by $E_G = h/t$, a version of the uncertainty principle. E_G is the gravitational self-energy of the superposition (the energy required to separate a particle, or its equivalent spacetime geometry from itself by separation distance s), h is the Planck–Dirac constant, and t the time at which OR reduction will occur. Each OR self-collapse chooses classical states, and is accompanied by a quantized protoconscious experience—a quale. (A distinction between protoconscious OR moments and fully conscious Orch OR moments will be discussed later.) Thus, consciousness is seen as a process on the edge between quantum and classical worlds.

In the Copenhagen interpretation, postcollapse states selected by conscious observation are chosen randomly, probabilistically (the Born rule, after physicist Max Born). However in Penrose OR the choices (and quality of subjective experience) are influenced by—resonate with—what Penrose called noncomputable Platonic values embedded in the fine scale structure of spacetime geometry. These Platonic values, patterns, or vibrations in the makeup of the universe, may encode qualia, and pertain to mathematics, geometry, ethics, and aesthetics, and the 20 or so dimensionless constants governing the universe. These include the fine structure constant, the mass ratios for all fundamental particles, the gravitational constant and many more, all precise to many decimal points.

If these numbers were slightly different, life and consciousness—at least as we know them—would be impossible. As described in the Anthropic principle (AP), the universe is fine-tuned for consciousness and life. But how and why these key values are so precise are unknown, and approached by several versions of the AP. In strong AP (Barrow and Tipler, 1986), the universe is somehow compelled to harbor and enable consciousness. The weak AP (Carter, 1974) suggests there exist multiple universes, and that only this particular one harbors conscious beings able to ponder the question. The weak AP is often aligned with MWI or multiverse concepts.

Penrose OR avoids the need for MWI and supports strong AP, suggesting that over aeons, dimensionless constants defining the universe evolved and self-organized to optimize life, qualia, and consciousness. How could that have happened? What *is* life?

LIFE IN THE QUANTUM UNDERGROUND

Life has been described in two types of general approaches: functionalism and vitalism. Functionalism characterizes life by its behaviors, including (from Lynn Margulis Sagan, 1995) self-organization, homeostasis, metabolism, growth, adaption, response to stimuli, replication/reproduction, and evolution. Richard Dawkins (1989) focuses on self-replication as life's essential feature, but all these functions occur also in nonbiological computer programs, eg, as artificial life (eg, Langton, 1995), video games, and weather patterns.

Living systems seem to have some unitary quality, akin to oneness, often ascribed to an emergent property of functional processes, much like consciousness is often ascribed to emergence from complex brain computation. In both cases, however, mechanisms, or thresholds for such emergence, are unidentified.

On the other hand, 19th century vitalists saw a unifying energy field, or life force pervading living systems—élan vital. As molecular biology developed, reductionists pushed vitalism from favor, the notion of a life force becoming taboo. But 19th-century vitalism was based either on electromagnetism, or on forces outside science, as quantum mechanics had yet to be discovered. In his famous book *What is Life?*, Erwin Schrödinger (1935) suggested life's unitary oneness derived from quantum coherence in biomolecular lattices which were aperiodic crystals.

Others agreed. Nobel laureate Albert Szent-Gyorgyi (1960) saw the essence of life in coordinated submolecular quantum electron movements in nonpolar regions of biological systems. Russian physicists Phillipe and Albert Pullman (Pullman and Pullman, 1963) attributed life to quantum behavior of electrons in pi resonance clouds, and biophysicist Herbert Frohlich (1968, 1970, 1975) described the essential unifying feature of living systems as quantum coherent dipoles in nonpolar regions in geometrically constrained proteins (eg, membrane proteins and cytoskeleton).

How could quantum coherence relate to cognition and consciousness? The concept of a quantum computer was introduced by Richard Feynman (1986), Paul Benioff (1982), and David Deutsch (1985), who showed how superpositions, eg, of both 1 *and* 0 bit states could act as quantum bits, or qubits, entangle and collapse/reduce to classical bits of either 1 *or* 0. But technological qubits require isolation and extreme cold to avoid decoherence, thermal disruption of seemingly delicate quantum superpositions (or premature OR in the Penrose approach). Consequently, living systems have been considered too warm, wet, and noisy for functional quantum mechanisms. However, photosynthesis proteins utilize quantum coherence, and microtubules and their component protein tubulin have quantum resonances in terahertz, gigahertz, megahertz, and kilohertz at ambient temperatures (Sahu et al., 2013a,b, 2014). But how can quantum systems self-organize, avoid decoherence, and govern biology in a warm and seemingly chaotic microenvironment?

The answer may be found in a simple truth: oil and water do not mix.

Consider a solubility phase perspective on the makeup of biological organisms. Rather than viewing living creatures as composites of tissues, cells, molecules, and atoms, they may be viewed instead as sets of various solubility

phases, ie, regions with different and distinct solvent characteristics, where particular molecules may bind and dissolve. Pharmacologists use solubility to determine where drugs bind in the body, an essential factor being degree of polarity, ie, how highly charged are the drug molecule (solute) and its environment (solvent).

Water, blood, and bodily fluids are polar solvents in which electrically charged solute molecules, eg, most drugs and hormones, bind and dissolve by hydrogen bonds and other polar interactions. In such microenvironments, quantum superpositioned charges will rapidly bind and entangle with others, increasing E_G to quickly reach OR threshold by $E_G = h/t$. OR events in such polar media, occurring ubiquitously, would be random, and accompanied merely by noncognitive, isolated moments of protoconscious experience (like dull, monotonous, and repetitious Whitehead occasions). Polar microenvironments are inhospitable to quantum superpositions.

However, the body and brain also include nonpolar, oil-like solubility phases, composed largely of benzene-like pi resonance clouds in aromatic rings which coalesce in nonpolar regions spatially segregated from polar ones (eg, oil and water do not mix!). Nonpolar groups bury themselves within protein, lipids, and nucleic acid molecules (eg, the pi stack in DNA), are friendly to quantum superpositions, and are the medium—the quantum underground—in which anesthetics specifically act to erase consciousness (see later in this chapter). Nonpolar regions are essential to organic chemistry, which starts with carbon.

Carbon atoms each have four electrons to bond with other atoms, eg, hydrogens and other carbons to form hydrocarbon chains called alkanes, with the general formula C_nH_{2n+2} where n is the number of carbons and length of the chain (Fig. 20.3). Carbons can also share two electrons, a double bond or pi resonance bond, and hydrocarbon chains with a single double bond are called alkenes, with the general formula C_nH_{2n}. Pi resonance implies a free electron (from carbon's outermost pi orbital) shared between carbon atoms, either oscillating between the two (molecular orbital theory), or delocalized, ie, in quantum superposition within a pi electron resonance cloud covering both carbons (resonance theory).

Nineteenth century chemists were puzzled by the structure of benzene, an oily, flammable hydrocarbon with the formula C_6H_6, fitting neither alkanes nor alkenes. Then the German chemist Kekule had a dream about snakes of varying lengths, which he later recognized as alkanes and alkenes. One longer snake in Kekule's dream swallowed its

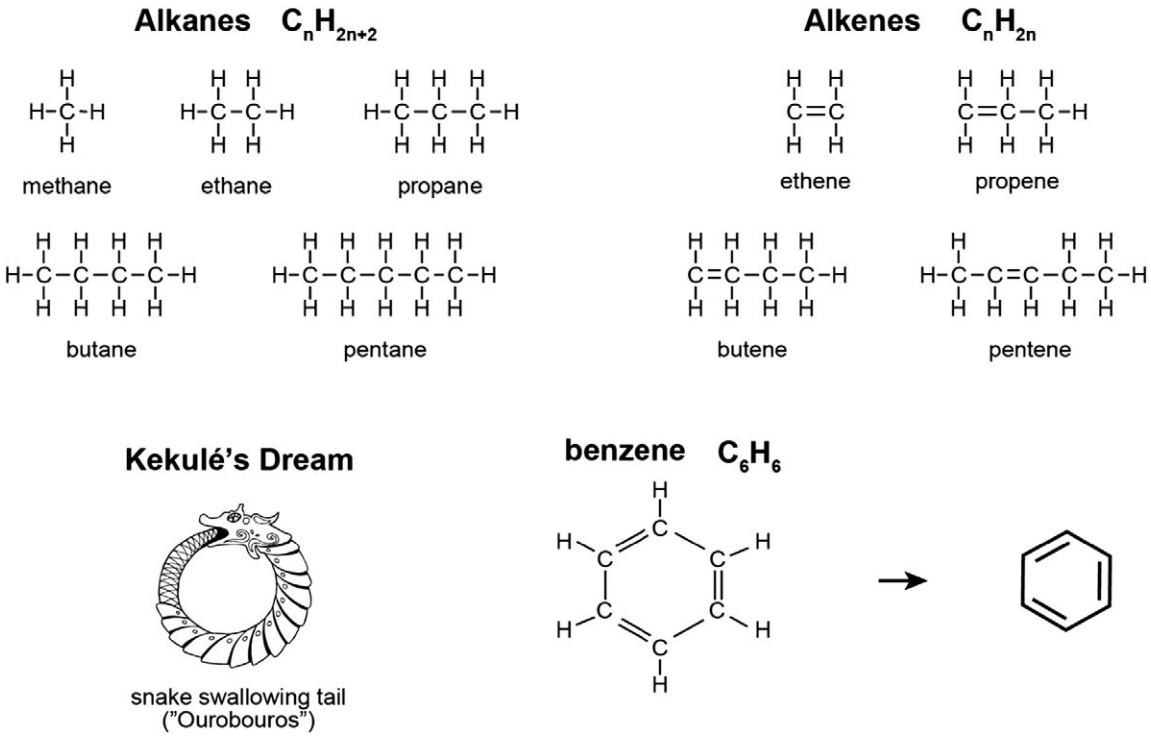

FIGURE 20.3 Carbon atoms can each form four covalent bonds, eg, with other carbons or hydrogens. Alkanes (top left) are a series of hydrocarbons with the general formula C_nH_{2n+2}. Alkenes (top right) are hydrocarbons with one carbon−carbon (pi resonance) double bond, and the general formula C_nH_{2n}. However, benzene had the formula C_6H_6 and was nonpolar and water-insoluble. Kekule's dream (lower left) suggested a ring structure which turned out to be correct with three carbon−carbon pi resonance double bonds. This is often represented as a hexagon with three extra bonds/lines (lower right).

tail, forming a ring (like the mythical Ouroboros). Kekule concluded it was benzene, C_6H_6, a hexagonal ring with three carbon−carbon pi electron resonance bonds.

Benzene's three pi resonance electrons are not confined to specific carbons, but delocalize and align in electron cloud dipoles which couple by van der Waals forces (or spin coupling), oscillate, and form superpositions (Fig. 20.4).

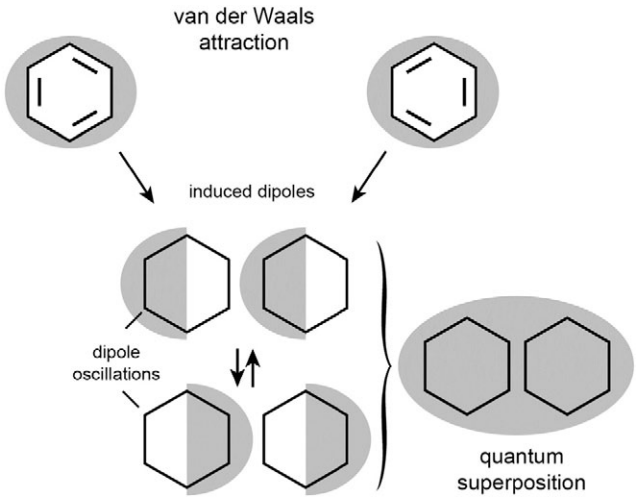

FIGURE 20.4 Electron resonance cloud dipoles of adjacent benzene (phenyl) rings can couple at precisely the proper separation distance (van der Waals radius), oscillate, and exist in superposition of both dipole orientations. Natural resonant frequencies for such rings are in terahertz (10^{12} Hz).

Pi resonance clouds are the basis for organic chemistry. Replacing hydrogens in benzene makes an attachable phenyl ring which, along with indole (6 + 5) rings are called aromatic because of generally sweet, pleasant smells. Adding one or more charged, polar ends to aromatic rings makes amphipathic biomolecules, nonpolar on one end, polar on another. They include aromatic amino acids phenylalanine, tyrosine and tryptophan, and psychoactive dopamine, serotonin,lysergic acid diethylamide, dimethyltryptamine, etc. (Fig. 20.5). When these bind to membrane receptors (or microtubules), nonpolar groups insert into nonpolar interior regions, and their charged, polar ends stick outward toward the exterior, forming a micelle structure. In bulk form, benzene is flammable and oily, but when geometrically constrained, eg, in flat sheets as graphene, or cylindrical fullerene nanotubes, pi electron resonance clouds couple in extended cooperative systems with interesting quantum properties (Figs. 20.6 and 20.7).

Though electrically neutral and nonpolar, pi electron resonance clouds are polarizable, and, when adjacent (at the angstrom-level van der Waals radius) attract and couple by induced quantum dipoles (van der Waals London forces, quadrupoles, magnetic dipoles). Such coupling is enhanced

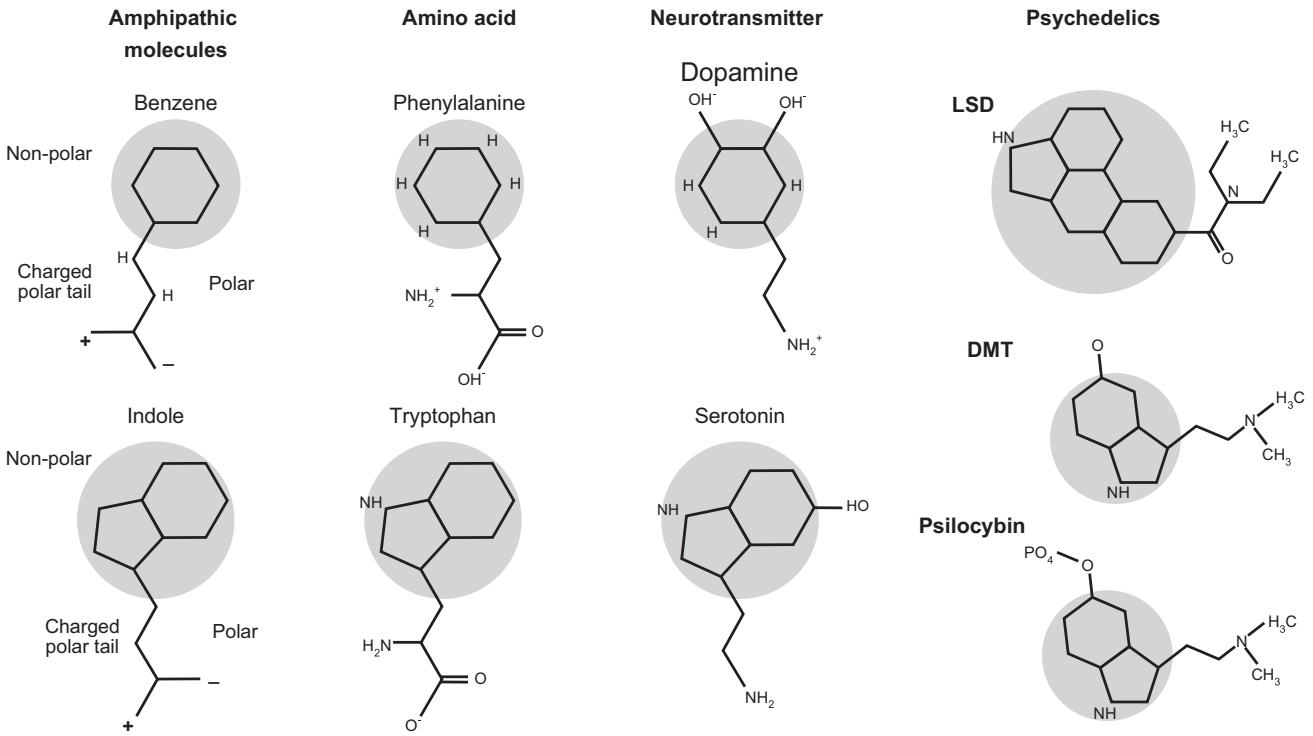

FIGURE 20.5 Amphipathic biomolecules have a nonpolar head composed of pi electron resonance clouds (gray) of phenyl (benzene) and indole aromatic rings, and tails with polar, charged ends. Virtually all psychoactive molecules are amphipathic including neurotransmitters and psychedelic drugs.

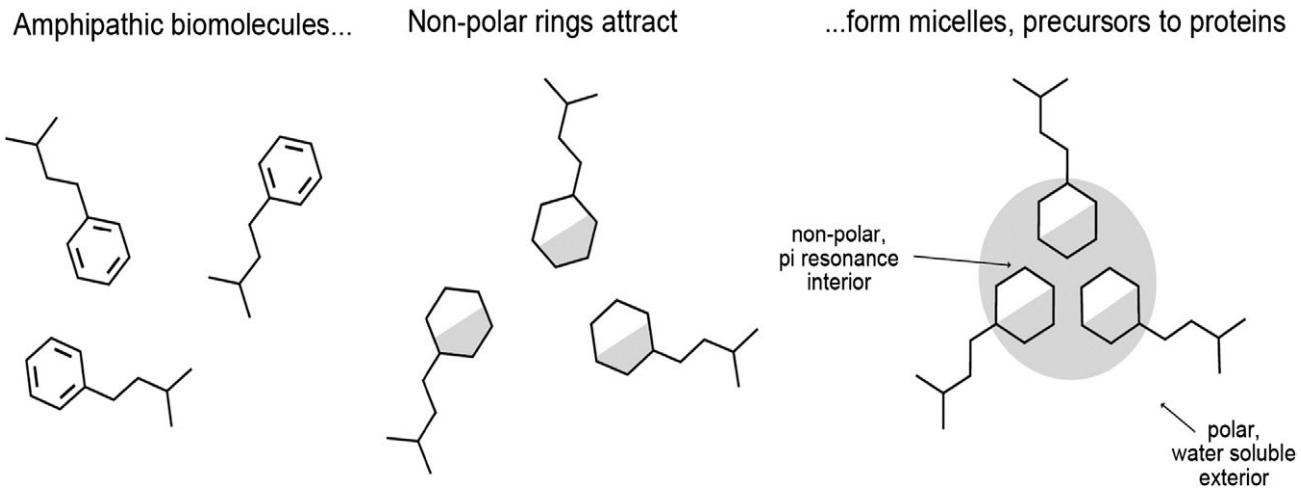

FIGURE 20.6 A simplified view of the origin of life. Amphipathic molecules (eg, in the primordial soup) attract and couple by van der Waals dipoles in a micelle (as suggested by Oparin) with a nonpolar interior and water-soluble exterior. Such structures are precursors to protein folding and formation of lipid membranes and nucleic acids (Fig. 20.7).

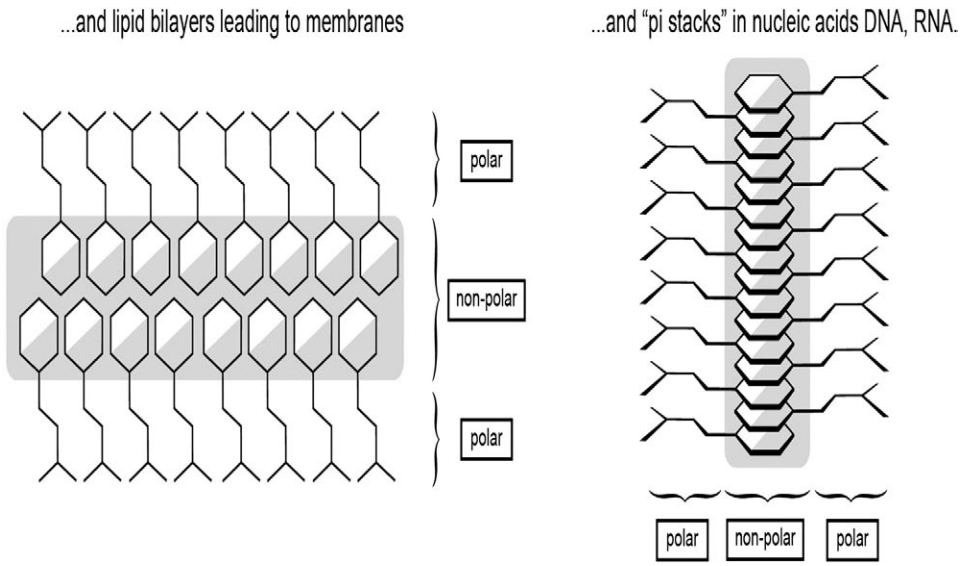

FIGURE 20.7 Amphipathic molecules form lipid bilayer (left) and nucleic acids DNA and RNA by similar mechanism, with nonpolar, water-excluding pi resonance quantum interiors, and polar, charged exteriors soluble in water.

by the hydrophobic effect (oil and water do not mix), which drives protein folding and results in pi stacking in which resonance rings are arrayed at specific spacings and geometric orientations. At the van der Waals radius, electron clouds can couple and oscillate by van der Waals London forces and excitons.

Quantum spin transfer through pi resonance clouds is enhanced by increased temperature (Ouyang and Awschalom, 2003), and pi resonance clouds are optically active and able to fluoresce, ie, absorb photons which induce excited electron states, and then emit lower energy photons when the excited states drop to lower states. This quantum-level energy can also be efficiently transferred nonradiatively between excited resonance clouds separated by up to 2 nm by Förster resonance electron transfer (FRET), or excitons. In plant photosynthesis, FRET-like excitons occur among seven or eight chromophores (more complex arrays of pi resonance rings) arrayed nanometers apart in Fenna-Matthews-Olson complex (FMO) proteins. Photons from the sun are collected in an adjacent molecule, converted to electronic energy, and transferred through FMO to a third molecule for conversion to chemical energy and food. The electronic energy transfer occurs through all chromophores simultaneously—a quantum superposition resulting in optimal efficiency. Life on earth depends on quantum coherence in photosynthesis proteins.

Tubulin proteins comprising microtubules (discussed later in Section: Microtubules and Sex in the Primordial Soup) each have eight tryptophan indole rings arrayed in a geometry strikingly similar to that in FMO photosynthesis proteins. Using molecular modeling, Craddock et al. (2014, 2015) showed FRET-like excitons passing through tubulin among eight tryptophan pi resonance clouds, driven by ambient energy, and blocked by anesthetics which bind naturally in nonpolar regions.

Interiors of DNA and membranes have similar arrays and stacks of pi resonance clouds and nonpolar regions. Taken together, a quantum-friendly, nonpolar solubility phase of pi electron resonance—a quantum underground—is shielded inside biomolecules, distributed throughout living systems, and hospitable to quantum superposition. Compelling evidence from anesthesia research directly links consciousness to this quantum underground.

In the mid-19th century, gases, such as diethyl ether and nitrous oxide ("laughing gas") were discovered to have anesthetic properties, ie, inhaling these gases caused humans and animals to lose consciousness, or some observable correlate, eg, mice falling over, or salamanders not moving in response to stimulation. When the anesthetic gas was exhaled away, the subjects and animals woke up, snapping back to consciousness, essentially unchanged. Potencies were determined for each anesthetic, ie, the gas concentration at which half of a group of mice, or salamanders, will roll over, and half remain upright. Amazingly, each gas acted at the same concentration in all animals, identical concentrations anesthetizing a mouse, salamander, or human. By the turn of the 20th century, dozens of anesthetic gases had been discovered, curiously with various different types of chemical structures, eg, ethers, halogenated hydrocarbons, nitrous oxide, and the inert gas xenon. Scientists sought a common molecular property, independent of structure, which correlated with anesthetic potency. The answer was solubility in an oil-like, nonpolar solubility region, in a quantum underground of pi resonance clouds.

Working separately, Hans Meyer (1901) and Ernst Overton (1901) ranked anesthetic potency for many anesthetics in various animal models, and tested anesthetic solubility in different types of solvents, each finding the same result. Over many orders of magnitude, among many chemically disparate structures, potency of all anesthetics for all animals correlated near perfectly with their solubility in a particular nonpolar medium, characterized by a low Hildebrand coefficient lambda (15.2−19.3 SI Units), closely resembling olive oil and benzene (Hameroff, 2006). The Meyer−Overton correlation shows that anesthetics act (by quantum London dipole dispersion forces), in nonpolar regions involving pi electron resonance clouds. As anesthesia is fairly selective (eg, sparing nonconscious brain activities which continue during anesthesia), consciousness apparently originates in pi resonance cloud regions in the quantum underground.

If so, the environment-hosting consciousness—the Meyer−Overton quantum underground—may have hosted the origin of life.

A general consensus is that life on earth began in a prebiotic primordial soup, proposed independently in the 1920s by the Russian biologist Alexander Oparin and British geneticist J.B.S. Haldane. The soup refers to a simmering mix from which life's biomolecular building blocks could have emerged three to four billion years ago, the requirements being an oxygen-poor atmosphere (now known to have been the case at that time), sea water, an energy source (eg, sunlight, heat, radiation, thermal vents, lightning), and necessary chemical components. In a famous experiment in the 1950s, chemistry graduate student Stanley Miller and his professor Harold Urey (Miller and Urey, 1959) simulated the primordial soup with methane, ammonia, hydrogen, and electric sparks for lightning. They found amphipathic molecules having both polar and nonpolar components, including pi resonance rings. These were apparently the seeds of life. But then what happened?

Richard Dawkins (1986, 1989) suggests molecular self-replicators carried life until genes and evolution were in place (cf, Dennett, 1995). RNA molecules, with stacks of nonpolar pi resonance clouds as central cores, may have acted as self-replicators. But if so, how and why did amphipathic replicators become functional and interactive?

Oparin had suggested amphipathic molecules formed micelles in which nonpolar parts of the molecules, eg, aromatic pi resonance rings, stick together in the micelle interior by van der Waals forces and hydrophobic effects (oil avoiding water). Polar ends of these same amphipathic molecules would then radiate outward from the central nonpolar confluence, forming hydrogen bonds with surrounding water. This process can result in water-soluble, spheroidal micelles, precursors to proteins and nucleic acids which are non-polar on the inside, and polar on the outside (Figs. 20.6−20.9). Oparin suggested micelles gained functions and began to organize, evolve, and function as protocells. But why would they?

Micelles have self-organized in laboratory experiments and are considered by some to be primitive forms of artificial life (Rasmussen, 2010). In some cases, optically active components are included in the nonpolar (quantum-friendly) interior (Rasmussen, 2010; Tamulis and Grigalavicius, 2014), enabling quantum entanglement between adjacent micelles.

Electric and magnetic dipoles of pi resonance clouds oscillate in terahertz (10^{12} Hz) in the infrared region of the optical spectrum. As the earth cooled, terahertz radiation in thermal noise could have driven pi stack oscillations in

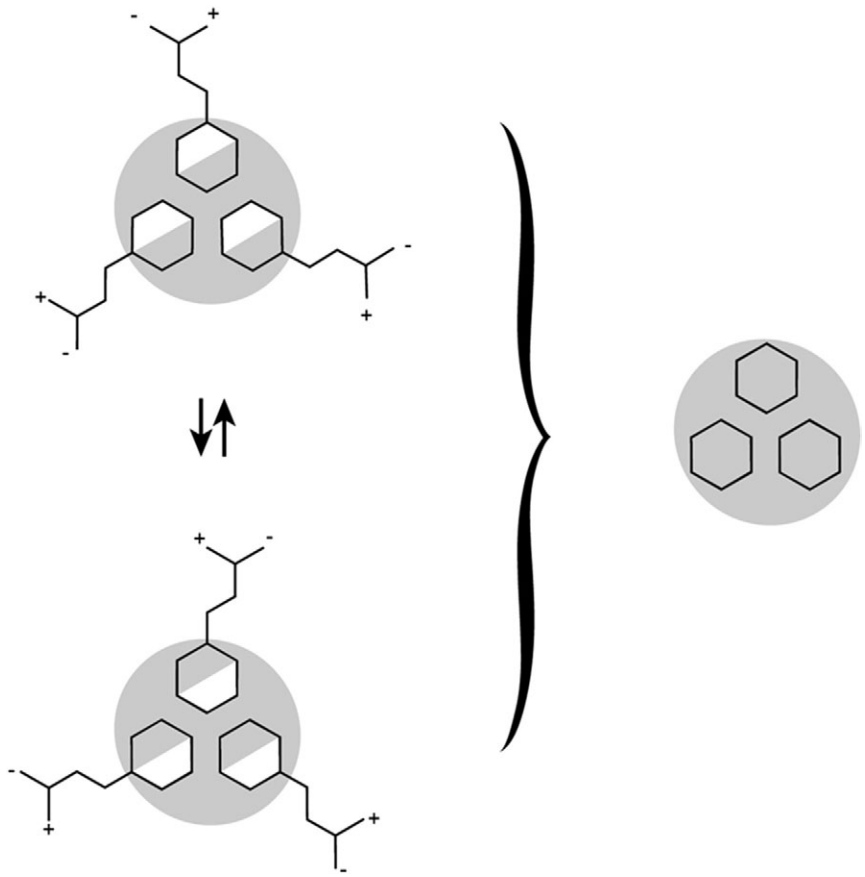

FIGURE 20.8 Simplified micelle qubit (only three amphipathic molecules are shown as opposed to hundreds or thousands). Left: Dipoles in nonpolar interior of Oparin micelle oscillate, eg, in terahertz. Right: Dipoles exist in quantum superposition of both possible states. Taken together the micelle is proposed to function as a quantum bit, or qubit.

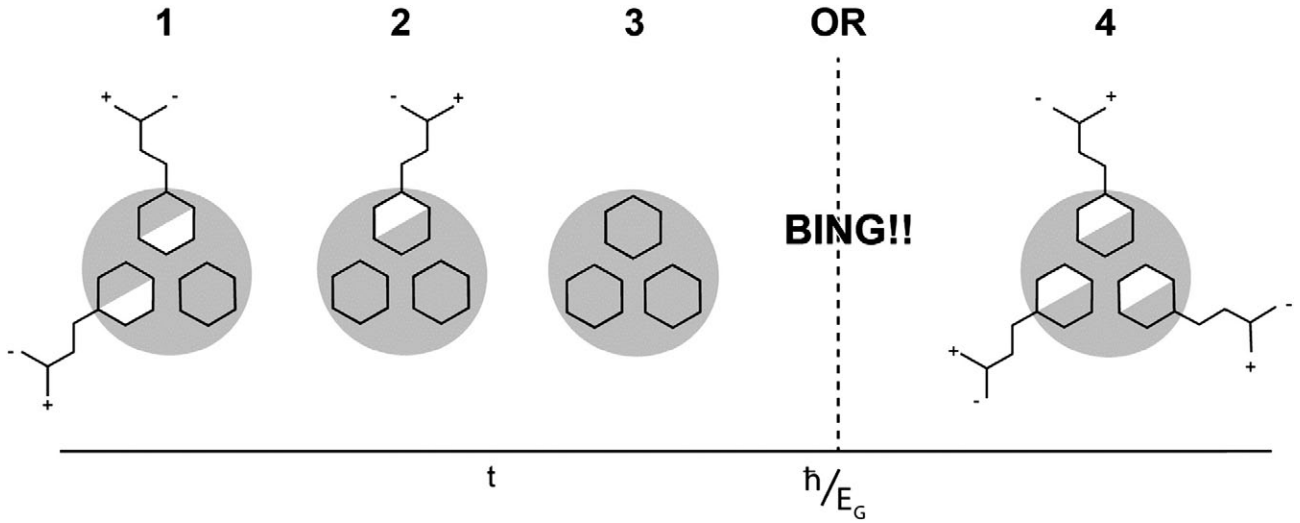

FIGURE 20.9 A simplified version of a protoconscious OR moment in the primordial soup. Three amphipathic molecules coalesce by nonpolar van der Waals attractions (polar tails disengage) and entangle in superposition to reach threshold for OR self-collapse at time $t = h/E_G$. A quale, protoconscious moment, or primitive feeling (BING) occurs. However, simple micelles as depicted here would rapidly entangle with the polar environment and undergo OR/decoherence to result in protoconscious moments with random qualia lacking cognition or meaning. Much larger micelles, eg, with many more pi resonance clouds forming a protected quantum underground would be required.

primitive micelles which became essential features of life. Vattay et al. (2015) have shown that pi resonance clouds are arrayed at precisely critical distances from each other in proteins to be at the edge between quantum and classical behaviors, ie, the separation distance at which mechanical vibrations can bring the groups into, and out of, quantum coherent superposition. Graphene (a planar layer of pi resonance rings) acts as a terahertz antenna, transferring up to 100 terabits per second. But the question remains why micelles or other structures based on pi resonance clouds with quantum properties would purposefully self-organize. There were no genes, no mutation-based evolution, no reward, no feedback, no creatures to survive. What was the motivation, the fitness function toward which life evolved? Was there a spark of life? If so, what could it be? A possible, logical answer is feelings, eg, pleasurable qualia occurring by Penrose OR.

Superpositions with electric charge in a polar, aqueous medium, eg, on micelle exteriors, would rapidly entangle by charge interactions to reach OR threshold with strictly random inputs. Such OR events would culminate in fleeting, noncognitive, protoconscious moments—quantum noise, in a musical metaphor. However, in nonpolar confluences of pi electron resonance clouds, shielded and precisely arrayed in the quantum underground, superpositioned dipoles could entangle collectively, oscillate coherently, and couple to biomolecular mechanical resonances—a coherent dance of quantum dipoles.

Superposition and coherence of just a few pi stack rings (small E_G) would require a long time t to reach threshold (by $t = E_G/h$). Polar interactions would likely intervene to contribute randomness, resulting in partially coherent moments of protoconscious experience (Fig. 20.9). With larger pi stacks protected in nonpolar quantum underground interiors of biomolecules and micelle-like structures, resonance with Platonic vibrations in spacetime geometry could occur so that associated protoconscious qualia would begin to have primitive feelings and emotions. The intensity and quality of such feelings, eg, pleasure, would depend on particular geometry of the pi stack (Fig. 20.9).

From Epicurus in ancient Greece to Freud's pleasure principle, and more recently Panksepp, Peil, and Damasio, feelings and emotions are considered primary in human and animal awareness and behavior, exemplified by dopaminergic reward pathways. But the essential nature of emotions, their subjective feel, remains a mystery. Why do good feelings feel good? Plato believed value, meaning, and pleasure to reside in the "form of the good," implying inherent geometry. Penrose attributed Platonic forms and values to fundamental spacetime geometry, extending to the Planck scale. Biology is based on organic chemistry, in turn based on pi electron resonance clouds of phenyl, or benzene rings. Dopamine, the pleasure molecule, is a prototypical amphipathic pi resonance phenyl ring molecule, presumably present in the primordial soup. Perhaps OR events, in particular pi resonance geometries, resonate more deeply with Plato's form of the good; encoded as vibrations in the structure of the universe, these events having feelings of greater pleasure. Such positive qualia—"good vibrations"—could have been the feedback fitness function by which life developed, with natural selection and survival of the fittest serving to optimize feelings. Feeling good by pleasurable OR could have been the spark of life by resonating with Platonic values embedded in the structure of the universe. Did biology then evolve to orchestrate OR, to turn quantum noise into conscious music, to "strike up the band?" To feel good? How could that have happened?

OR is naturally causal, choosing among different possibilities, a requisite for intentional purpose. In a nonpolar environment (the quantum underground) adjacent pi resonance rings, attracted by van der Waals London force dipoles and quadrupoles tend to align in one of two stable orientations, separated by the van der Waals radius. The two stable orientations are the "T," in which one ring hangs perpendicular from the middle of the second ring, and the offset parallel (OP) orientation, in which two rings are parallel in one plane, and offset.

OR events from various configurations would result in specific superpositions of pi resonance clouds and particular rudimentary mental experiences. Thus, arrangements of pi stack orientations can be a code for qualia. Adjacent pi resonance rings may be arrayed as T or P, so a stack of three rings would have four possible arrangements, P—P, T—T, T—P, and P—T. When superposition and OR results by $E_G = h/t$ among these rings, particular qualia (eg, good, bad) would occur. For example, P—P might have pleasurable feelings, and T—T unpleasurable ones. With causal effects of OR outcomes influenced by feedback, three-dimensional pi stacks could then rearrange in orientation sequences (including helical, branching, and different ring types) to optimize and orchestrate OR-mediated feelings and qualia. Over time and replication cycles, recurrent feedback could optimize pi stack geometry for pleasurable conscious feelings whose particular pi-stack orientations would best resonate with Platonic values in spacetime geometry.

Micelle-like structures, RNA, membranes, and other structures in the primordial soup could self-organize their pi stacks to optimize OR qualia. But pleasure, and ability to causally affect the physical world to further increase pleasure, would soon become limited. Better organization, memory, motility, communication, and reproduction were required to feel even better. Self-assembling intelligent polymers were the answer.

Enter microtubules.

MICROTUBULES AND SEX IN THE PRIMORDIAL SOUP

Interiors of all animal cells are organized and shaped by the cytoskeleton, a dynamic scaffolding of protein lattice polymers. These self-organizing structures include microtubules, microtubule-associated proteins (MAPs), actin, and intermediate filaments, all anchored by the centriole, a pair of microtubule-based mega-cylinders in the cell center (centrosome), just outside the nucleus. Plant cells also have microtubules and centrioles, and prokaryotes and archaebacteria have similar, but slightly different protein structures. All living cells are organized by microtubules or closely related structures.

Microtubules (MTs) are cylindrical polymers 25 nm ($nm = 10^{-9}$ m) in diameter, comprised usually of 13 longitudinal protofilaments, each a chain of the protein dimer tubulin. Composed of alpha and beta monomers with net dipoles, tubulins give microtubules net dipoles. Tubulins self-assemble and arrange in MTs in two types of twisted hexagonal lattices (A-lattice and B-lattice) such that helical pathways along contiguous tubulins in the A-lattice repeat every three, five, and eight rows on any protofilament (the Fibonacci series). Within microtubules, each tubulin may differ from its neighbors by genetic variability, posttranslational modifications, phosphorylation states, binding of ligands, and MAPs, and transient dipole orientation (Hameroff, 1987; Garham et al., 2015). With many tubulins per cell, eg, 10^9 tubulins per neuron, information capacity in a mosaic-like MT is enormous. Epigenetic information is encoded in microtubule-based centrioles (Balestra et al., 2015).

Due to their organizational roles, lattice structure and coherent dynamics, microtubules have been suggested to actively process information since Sherrington (1951) described them as the cell's nervous system. Descriptions of MTs as computer-like devices (Hameroff and Watt, 1982; Hameroff, 1987; Rasmussen et al., 1990) viewed individual tubulins as bit-like information units in Boolean switching matrices, or cellular (molecular) automata played on microtubule lattices. Simulation of tubulin dipoles interacting with neighbor dipoles and synchronized by Fröhlich coherence showed rapid information integration and learning (microtubule automata; Smith et al., 1984; Rasmussen et al., 1990; Fig. 20.10).

Microtubules in neurons seemed particularly suited for memory and some form of computation. In cell division (mitosis), MTs disassemble and then reassemble as mitotic spindles, anchored by centrioles, which separate chromosomes, establish daughter cell polarity, and rearrange for cellular structure and function. However, neurons do not divide once they are formed, and so neuronal microtubules can remain assembled, providing a stable medium for memory encoding.

Microtubules in neuronal soma and dendrites are unique in other ways. In axons, and all nonneuronal cells throughout biology, microtubules are arrayed radially, like spokes in a wheel, extending continuously from the hub-like centriole outward toward the cell membrane, all with the same polarity. However, microtubules in dendrites and cell bodies/soma are short, interrupted and arrayed in mixed polarity networks interconnected by MAPs, and stabilized by MAP-capping proteins. Interrupted dendritic-somatic microtubules are poorly suited for structural support, but ideal for memory encoding and information processing (Rasmussen et al., 1990).

The standard explanation for memory encoding in neuroscience is synaptic plasticity, ie, sensitivities at particular synapses guiding activity through neuronal networks. However, synaptic proteins are transient and

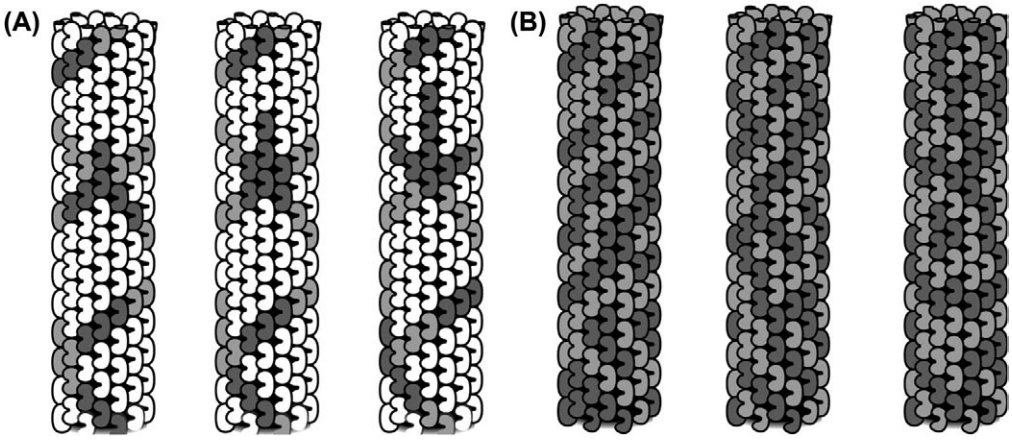

FIGURE 20.10 Three time-steps (eg, at 10 MHz) of a microtubule automaton which is classical. Tubulin subunit dipole states (light gray, dark gray) represent information. (A) Spin currents interact and compute along spiral lattice pathways. For example (upper, middle in each microtubule) two upward-traveling spin waves intersect, generating a new vertical spin wave (a "glider gun" in cellular automata). (B) A general microtubule automata process. *With permission from Hameroff, S., Penrose, R., 2014a. Consciousness in the universe: a review of the 'Orch OR' theory. Physics of Life Reviews 11 (1), 39–79.*

recycled over hours to days, and yet memories can last lifetimes. Craddock et al. (2012b) showed how synaptic information in the form of calcium ion influx activates the hexagonal enzyme calcium-calmodulin-kinase II (CaMKII), which can then encode up to 6 bits of information on microtubules by phosphorylation (Fig. 20.11).

Synaptic proteins are synthesized in neuronal cell bodies/soma, and transported to synapses by dynein and kinesin motor proteins traveling along microtubule tracks. In interrupted dendritic-somatic microtubules, motor proteins must jump from microtubule to microtubule, and choose particular pathways at synaptic branch points to deliver synaptic cargo. Delivery is guided by specific placement of tau on microtubule lattices as "traffic signals" or address code (Dixit et al., 2008), getting the right cargo to specific synapses, serving memory and cognition. Displacement of tau from microtubules results in neurofibrillary tangles, microtubule instability, and the cognitive dysfunction in Alzheimer's disease. CaMKII may encode tau binding on microtubule lattices following synaptic calcium influx (Craddock et al., 2012b). Dendritic-somatic microtubules are likely and convenient sites for memory encoding, cognition, and consciousness.

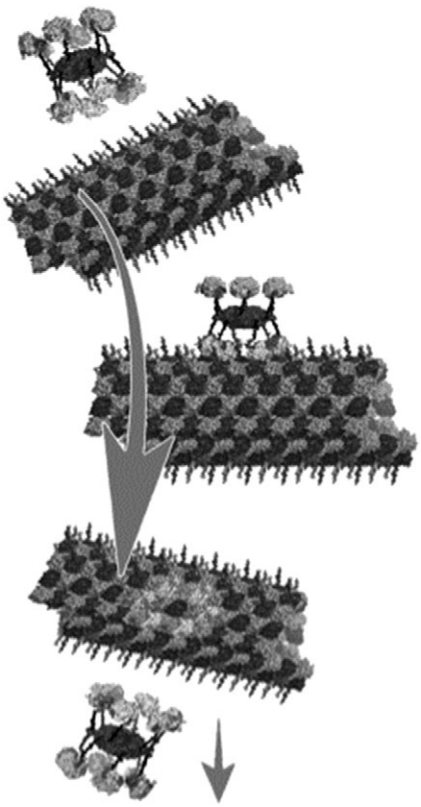

FIGURE 20.11 Calcium-calmodulin-kinase II (CaMKII), a hexagonal holoenzyme activated by synaptic calcium influx extends six leg-like kinase domains above and below an association domain. The six kinase domains precisely match hexagonal size and geometry in both A-lattice and B-lattice microtubules. *With permission from Travis.*

Microtubule-based processing implies a huge increase in cellular and brain-wide information capacity. For example, artificial intelligence (AI) proponents (including advocates of the Singularity) aim to emulate the brain in computers, and estimate brain capacity as 10^{11} neurons, each with 10^3 synaptic connections firing, or being excited up to 100 times per second (10^2 Hz), giving a capacity of 10^{16} operations per second for the brain. But inside each of those neurons are microtubules with 10^9 tubulins/neuron capable of switching at 10^7 Hz (Sahu et al., 2013a,b, 2014), for 10^{16} operations per second per *neuron*, and 10^{27} ops/s for the brain. Microtubule information processing would push the AI/Singularity goal for brain equivalence in computers far into the future, and can account for memory. But increased capacity per se does not address the hard problem of consciousness, of subjective feelings, of qualia. The only specific scientific mechanisms for qualia, feelings, and subjective conscious experience which has ever been proposed is Penrose OR.

In the mid-1990s, Sir Roger Penrose and I began to suggest that microtubules could act as quantum computers whose superpositioned qubits would halt, or terminate to classical states by quantum state reduction—"collapse of the wave function," according to Penrose OR. Such events would have cognitive representation and meaning by virtue of microtubule information processing, unify or bind percepts by entanglement, and have phenomenal experience, or qualia, at each moment of OR. Through information processing, memory, and natural resonances, brain microtubules would orchestrate OR events into full, rich conscious moments (Orch OR). Metaphorically, random, meaningless OR notes, sounds, and noise qualia become meaningful music.

The qubit for Orch OR microtubule quantum computing was originally suggested to utilize superposition of alternate states of individual tubulins, interacting with surrounding neighboring tubulins in hexagonal cellular automata. When the atomic structure of tubulin became known through crystallography in 1998 (Nogales et al., 1998), clusters and channels of pi electron resonance clouds of aromatic amino acids became apparent (Fig. 20.12). Quantum transfer of electronic excitations and dipole resonance among arrays of pi resonance clouds were proposed to occur within tubulin, and also between and among neighboring tubulins in helical pathways in microtubule lattices, eg, the five-start and eight-start helices of the Fibonacci sequences in microtubule A-lattices. Accordingly, net dipole orientations along helical pathways were proposed to act as Orch OR qubits, along the lines of topological quantum computing.

The Orch OR proposal in the mid-1990s prompted skeptical criticism, largely based on decoherence, the notion that thermal vibrations would disrupt seemingly delicate quantum processes. Laboratory efforts to build

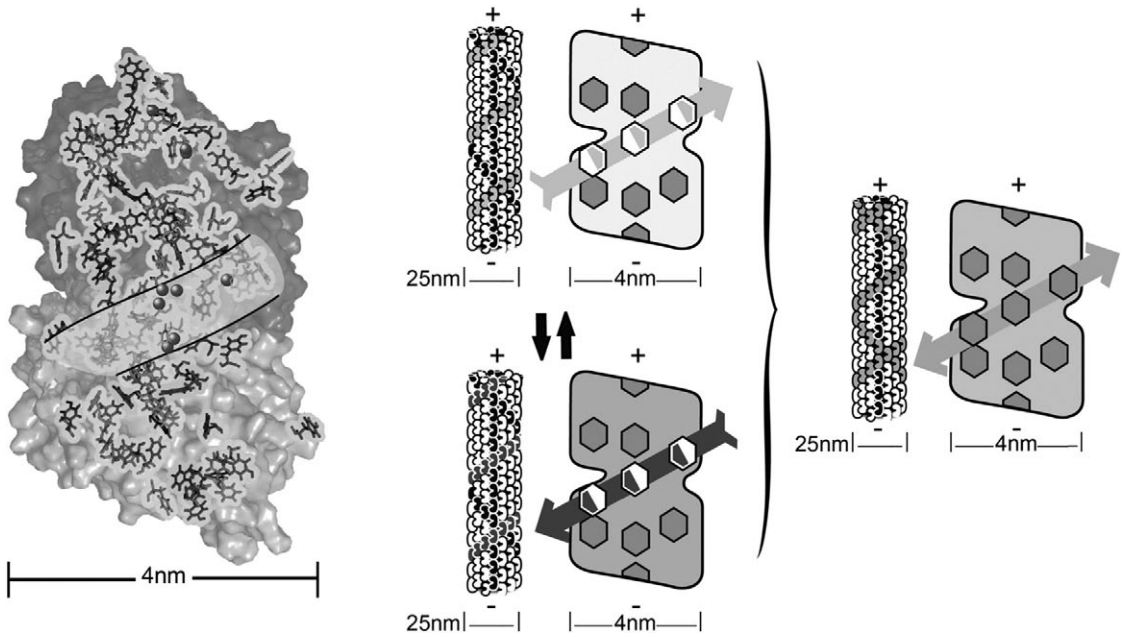

FIGURE 20.12 At left is the protein tubulin showing aromatic amino acid pi resonance clouds (tryptophan, phenylalanine, tyrosine) and sites of binding of anesthetic halothane (spheres). Band indicates nonpolar cluster of aromatic rings (quantum channel or quantum underground) with anesthetic binding sites aligned along five-start helix in microtubule lattice. Right: Dipole qubit in microtubule in Orch OR theory, with quantum dipole states oscillating, and forming quantum superposition of alternate states along five-start helical pathway in tubulin and microtubules. Dipoles may be electric or magnetic, eg, related to electronic (and/or nuclear) spin. Similar qubit pathways may occur along eight-start pathways or other pathways.

quantum computers were conducted near absolute zero temperature, and the brain (and biology in general) were considered too warm, wet, and noisy. However, beginning in 2007 (Engel et al., 2007), quantum coherence in plant photosynthesis at ambient temperatures was discovered, and found to depend on nonpolar (ie, dry, not wet) pi resonance groups, and coupling to coherent mechanical vibrations. As suggested by Frohlich (1968, 1970, 1975), thermal vibrations pumped the quantum coherent states, rather than disrupted them. Subsequently, Anirban Bandyopadhyay's group (Sahu et al., 2013a,b, 2014) found resonances in individual microtubules, and bundles of microtubules in self-similar patterns occurring every two to three orders of magnitude in terahertz, gigahertz, megahertz, and kilohertz frequency ranges (Fig. 20.13). Conductances in microtubules at these frequencies were determined to be quantum in nature because conductances through entire microtubules were greater (resistances lower) than through individual tubulin proteins. A picture emerges of microtubules as multiscalar biological quantum resonators.

The evolution of tubulin and microtubules is puzzling. Why would tubulin, a single protein, evolve as a cog in a machine, one brick in a skyscraper yet to be realized? According to conventional evolutionary theory, the feedback fitness function for tubulin would depend on higher order microtubule activities not yet present. Proponents of intelligent design cite microtubules and their composites cilia and centrioles as structures which are difficult to explain through natural selection. They may have a valid objection, but lack a scientific alternative.

How *did* tubulin and microtubules (or their prokaryotic and archaebacteria counterpart proteins) evolve? Consider a possible scenario in the primordial soup. Pumped by ambient terahertz radiation, pi resonance rings on amphipathic molecules coalesced, coupled, and oscillated in nonpolar micelle interiors. Van der Waals forces provided separation between rings at quantum critical distances (Vattay et al., 2015). As micelles incorporated more pi resonance clouds (eg, clusters of three or four rings), entangled quantum superpositions extended in an expanding quantum underground. The resultant increasing "E_G" in each $E_G = h/t$ OR event became, with feedback and developing over time, more purely coherent so that subjective protoconscious OR qualia became more cognitive and intense, good or bad. Good feelings ensued from more energetically favorable pi stack geometry which resonated with Platonic values.

Here is a possible scenario. As the number of coupled coherent rings and E_G grew, intensity and quality of good feelings also grew, providing feedback to pi stack geometry, eg, flipping T and OP configurations within each micelle's quantum underground, optimizing qualia and experience.

Rudimentary mental states exerted causal power, arranging pi resonance clouds within micelles which became

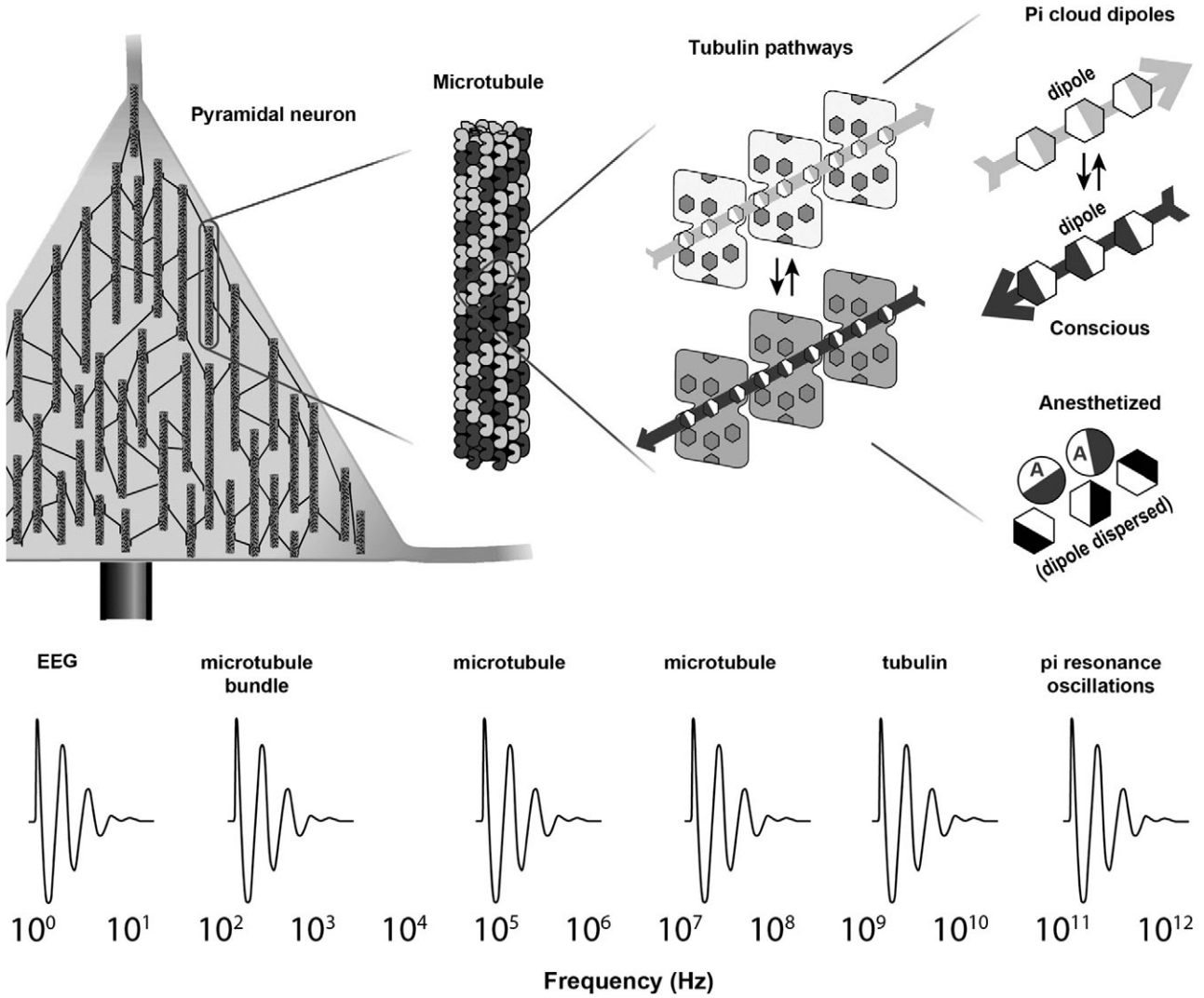

FIGURE 20.13 Brain multiscalar hierarchy. Top row shows structure (left to right) pyramidal neuron cell body with interior microtubules, a single microtubule, tubulin pathways through pi resonance clouds along which dipole oscillations, resonance transfers, and/or spin currents occur (top) pi cloud dipole oscillations (bottom) anesthetics dispersing dipoles. (Bottom) Dynamics at frequency ranges matching structure in top row (Sahu et al., 2013a,b, 2014, Craddock et al., 2015).

proteins, membranes, and nucleic acids. With repetitive feedback, clusters of pi resonance clouds optimized their geometry for pleasurable qualia as particular sequences of T and OP arrangements, coupling with other clusters by FRET and excitons, and absorbing and resonating with ambient terahertz, ultraviolet and cosmic microwave radiation. This all served to further optimize OR-mediated pleasure by pi cloud geometry.

But then what happened? Tubulins aligned by charge interactions and entropy, forming lattice patches with pi resonance clouds extending from one tubulin to its neighbor, increasing OR-mediated pleasure. Cooperative information exchange developed a logic based on hexagonal geometry of tubulin patches which rolled into cylinders, stabilized by ultra-violet absorption and megahertz mechanical resonances, reinforcing pi stack coherence, developing a hexagonal-based information code, ramping up OR pleasure even more. The microtubule was born.

Neighboring microtubules became interconnected by MAPs forming networks of coupled resonators. Coherent lattice vibrations enabled stable quantum coherence, as Fröhlich predicted in the 1970s. Mixed polarity networks were most conducive to cooperative resonance, leading to orchestrated OR events, interference beats, and faster, richer, and more intense moments of conscious experience. At much higher frequencies and smaller scale, these processes connect to fundamental spacetime geometry (Fig. 20.14).

Microtubules fused into doublets and triplets, further ramping up OR pleasure. These then aligned into megacylinders of nine doublets/triplets called cilia, centrioles,

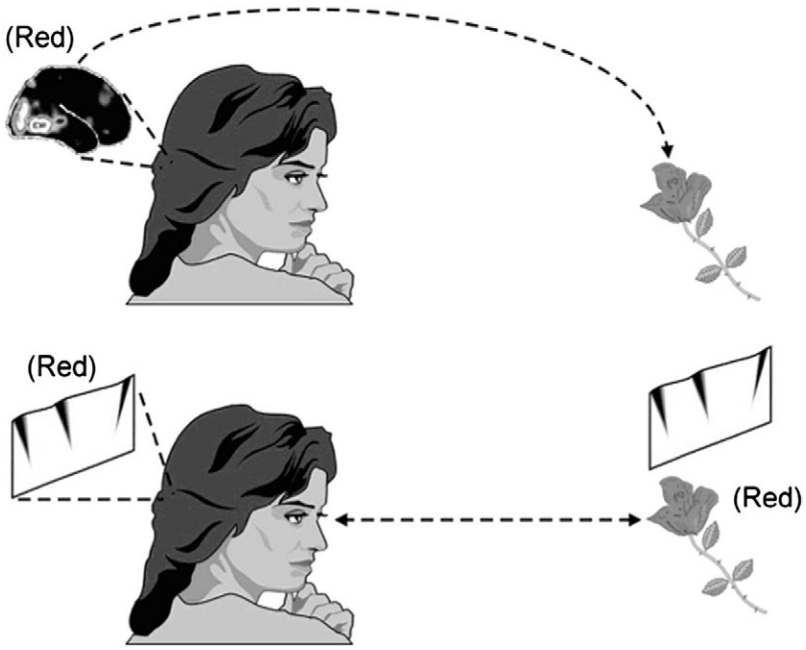

FIGURE 20.14 (Top) Conventional views characterize the redness of a rose as a particular pattern of brain activity. (Bottom) The Orch OR theory suggests redness is a particular pattern of curvature in fundamental spacetime geometry.

and flagella. Membrane-covered cilia and flagella acted as sensors, as well as motor-like oars and whip-like propellers, able to bend, move, and exert causal effects in their environment (the same mechanism moves synaptic cargo through brain neurons).

Centrioles, the focal point of the cytoskeleton inside cells, are two mega-cylinders arrayed in a mysterious perpendicular alignment, each with a helical twist. Centrioles organize and anchor mitotic cell division, the first step being to spawn another mega-cylinder, rotating perpendicularly. The original pair then separates, the daughter centrioles twisting through cytoplasm, leading spindles and chromosomes to perfect alignment and daughter cell destiny. Perpendicular rotational spawning allows centriolar information (as states of tubulin) to be transferred to subsequent generations without genes, epigenetic Lamarckian inheritance (Balestra et al., 2015).

Cilia, centriole, and flagellar composites of microtubules also gained new mechanical vibrations, further promoting quantum resonances, and became able to detect photons. Biologist Guenter Albrecht-Buehler (1992) isolated fragments of cells containing the centriole, cytoplasm, and enough cytoskeleton to move around, without nucleus or DNA. He then shone infrared light at the fragments which invariably turned and moved toward the light source. He meticulously showed it was the centriole mega-cylinders, 150 -nm inner diameter and ~700 nm in length, perfectly sized for optical wavelengths, which received and responded to the photons (Fig. 20.15). Primitive visual systems consist of ciliated ectoderm which, along with centrioles and flagella, may capture and detect photons, pumping FRET-like excitons and promoting OR pleasure qualia.

With membrane coats and metabolic machinery, solar-powered flagella became motile spirochetes, slithering through the primordial soup in search of nutrients and photons, catching rays and feeling good. OR pleasure jumped exponentially. Musically, vibrational resonance brought harmony, range, and tunes.

By then, simple immobile prokaryotic cells had also emerged with microtubule-like structures (FtsZ proteins), lacking movement and internal compartmentalization, their DNA and metabolic enzymes floating freely in watery interiors. According to biologist Lynn Margulis-Sagan (1995), prokaryotes underwent a series of symbiotic mergers to produce the eukaryotic animal cell, our ancestor. She proposed prokaryotes ingested mitochondria from another species, providing chemical energy in the form of ATP, mitochondria remaining on as sheltered intracellular organelles. Margulis-Sagan also suggested prokaryotes ingested, or were invaded by spirochetes—motile flagellates, much like sperm penetrating an ovum. The invading flagellates became symbiotic with their hosts, forming the cytoskeleton, eg, cilia, centrioles, flagella, and microtubules. Eukaryotic animal cells were able to sense their environment, move nimbly, and interact with other organisms (Fig. 20.16). As genes developed, cells became able to undergo mitosis. The cytoskeleton may have also brought intelligence, consciousness, and sexual reproduction.

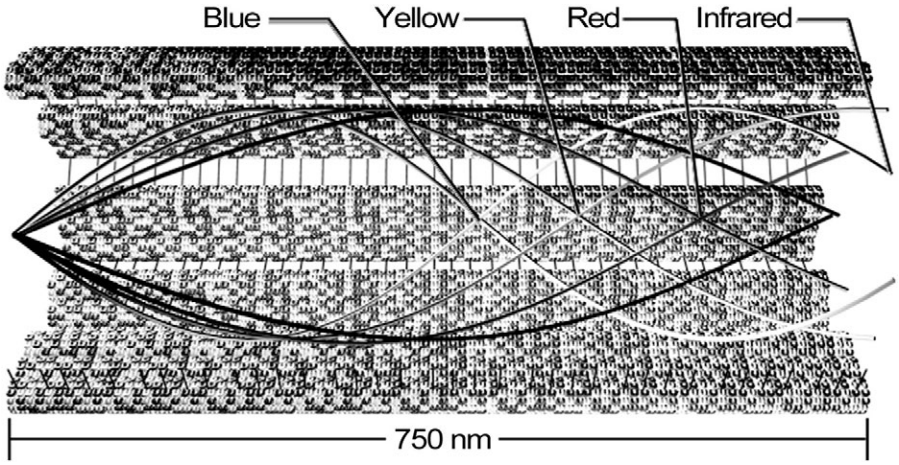

FIGURE 20.15 Inside of centriole/cilia structure shows five (of nine) microtubule triplets. Wavelengths of visible and infrared photons match interior cavity as waveguide/resonator. Centrioles and cilia are able to detect photons.

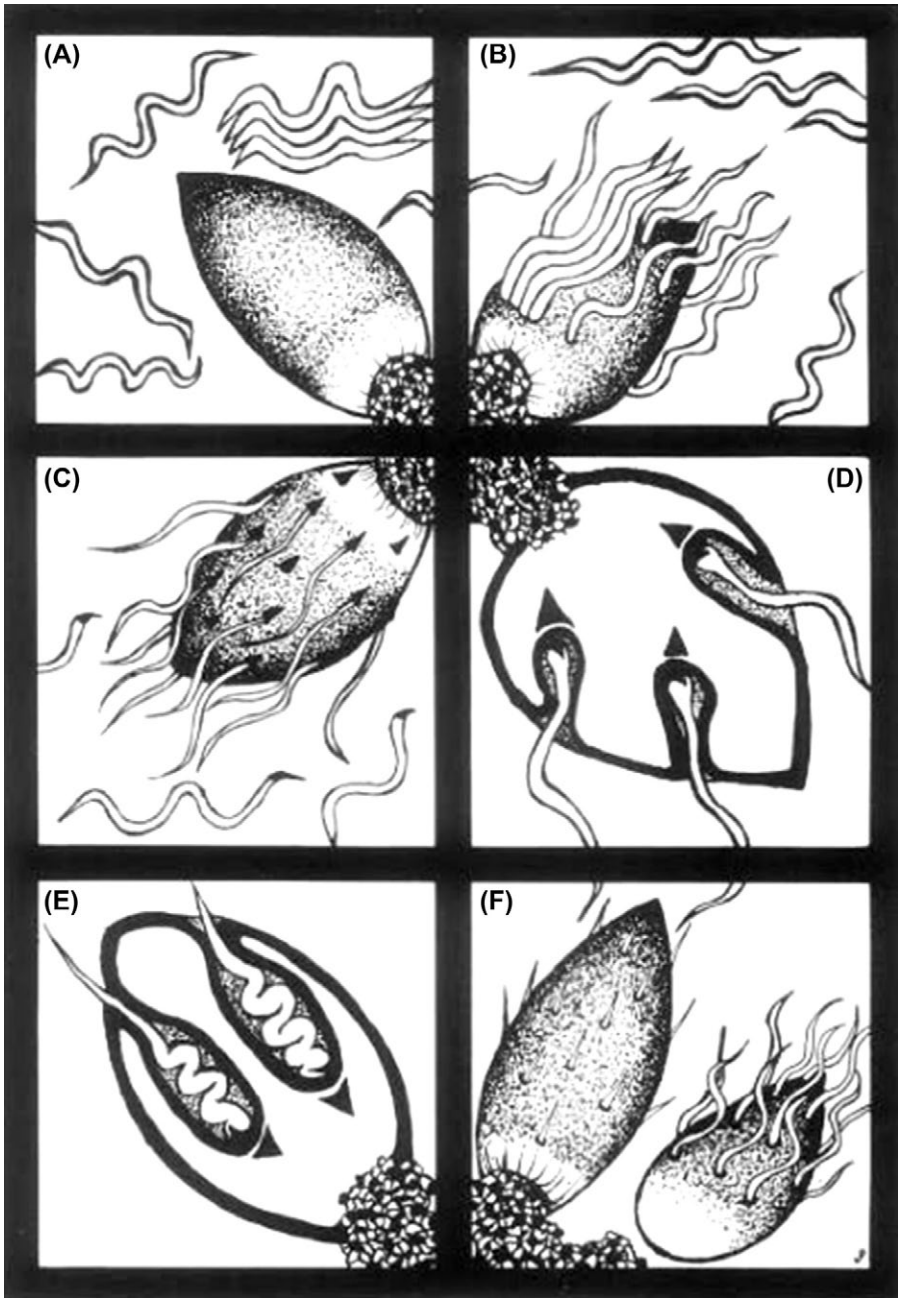

FIGURE 20.16 Symbiotic ingestion of/invasion by motile spirochetes into a primitive prokaryotic bacterium, resulting in the first eukaryotic cell. The spirochete's filamentous proteins became, according to Margulis-Sagan's endosymbiotic theory, the centrioles and cytoskeleton of eukaryotic cells, providing movement and organization of cytoplasm. *From Hameroff, S., 1987. Ultimate Computing-biomolecular Consciousness and Nanotechnology. Elsevier, Amsterdam by Paul Jablonka.*

Prokaryotes reproduce by simple division and budding to form spores. Spirochetes undergo longitudinal fission, separating along parallel microtubule doublets. With the onset of genetic material, sexual reproduction would eventually enable evolution, gene mixing, species diversification, and adaptability. But how did it start? Evolutionary biologists are unable to explain the origin of sexual reproduction and gender.

Graham Bell (1982) says "Sex is the queen of problems in evolutionary biology." Richard Dawkins' (1989) trademark "selfish gene" view finds sex "counter-productive, throwing away half one's genes with every reproduction." Ironically, Dawkins lists the origin of sex as one of three remaining mysteries in evolution, along with consciousness, and differentiation, the mechanism by which "genes influence bodies." All three mysteries can be explained through microtubules.

In *The Cooperative Gene*, Mark Ridley (2008) writes "Evolutionary biologists are much teased for their obsession with why sex exists. People like to ask, in an amused way, 'isn't it obvious?' Joking apart, it is far from obvious…. Sex is a puzzle that has not yet been solved; no one knows why it exists".

It *is* obvious. Sex feels good. Sex and sexual reproduction might have started through endosymbiosis, driven by the quest for OR pleasure. Flagellated spirochetes were likely the most agile and clever of creatures, marauders of the soup. Sedentary prokaryotes were inviting targets. In a manner analogous to sperm fertilizing eggs, spirochetes wriggled through cell walls to reach bacterial interiors, finding energy (eg, for dynein motors) and a stable, protected environment. Pi cloud arrays in host cell proteins coupled their E_G with that of flagellar microtubules, the mutual superpositions avoiding random distractions from the polar environment and allowing orchestration. OR threshold was approached more gradually, harmonically, with orchestrated pi stack coherent contributions. When threshold was finally reached by $E_G = h/t$, climactic and pleasurable Orch OR moments occurred. Sex was born.

At first, spirochetal invasions might have been temporary and predatory—one night stands. But spirochetal microtubules began to unpack, disassemble, and rearrange through quantum dipole coupling with host protein pi stacks. Microtubules moved in, further optimizing Orch OR resonance and mutual benefit and pleasure. The symbiosis took hold. Mitosis by centrioles and microtubule spindles separated chromosomes into perfectly paired matches, combining genes from each parent, promoting diversification and adaptation. These evolutionary processes have continued through the present day.

Microtubules radially arranged around centrioles, tethered by actin proteins in tensegrity structures in cell interiors. Rigid cell walls were replaced by flexible membranes. Megacylinder extensions in cilia, flagella, and axonemes enabled external sensing, agile locomotion, and adaptive interactions with other cells and the outside world. Within cell cytoplasm, centrioles and microtubules fostered mitosis, gene mixing, mutations (influenced by Penrose OR—mediated Platonic influences in DNA pi stacks) and evolution, all in pursuit of more and more pleasurable qualia. Cells began to communicate, compete and/or cooperate, guided by feedback toward feeling good.

Cells joined through adhesion molecules and gap junctions, resulting in multicellular organisms. Specialization occurred through differentiation via gene expression through cytoskeletal proteins. In some types of cells, the cytoskeleton became asymmetric and elongated, taking on signaling and management roles as axonemes and neurons. Neurons and other cells fused by gap junctions, and chemical signaling ensued at synapses between axons, and dendrites and soma within which microtubules became uniquely arranged in mixed polarity networks, optimal for integration, recurrent information processing, interference beats, and orchestration of OR-mediated feelings. Neurons formed networks, E_G grew larger, t grew shorter and conscious experiences became more and more intense. At E_G of roughly 10^{11} tubulins in $\sim$300 neurons or axonemes in simple worms and urchins, t became brief enough to avoid random interactions, prompting, perhaps, the Cambrian evolutionary explosion (Hameroff, 1998). The brain evolved in pursuit of pleasure, and in the musical metaphor, the band began to play.

CONCLUSION: DID "QUANTUM FEELINGS" SPARK THE ORIGIN AND EVOLUTION OF LIFE?

Darwin's theory of evolution through natural selection is a pillar of modern science, but it is incomplete. Natural selection fails to address the origin of life, the nature of consciousness, and presumed incremental changes in evolution cannot fully explain life's molecular machinery. Something is missing.

In modern times Darwin's theory is taken to imply (eg, Richard Dawkins' "selfish gene") that behavior of living organisms serves to promote genetic survival through reproductive success. But behavior in humans and animals is driven by conscious feelings (eg, Epicurean delight, Freud's pleasure principle, dopaminergic reward, avoidance of pain). The subjective nature of conscious feelings (phenomenal experience, or qualia in philosophical terms) has yet to be explained scientifically, theorists appealing to either higher order emergence, or lower level panpsychism, the latter suggesting qualia are intrinsic features of matter, or deeper levels of reality. These deeper levels somehow give rise not only to qualia, but also to matter, as well as electrical charge, magnetic spin, and the various constants and parameters which govern the universe. In approaching

these deeper levels another mystery arises, that of quantum mechanics and collapse of the wave function.

At small scales, particles exist in multiple states or locations simultaneously—quantum superposition, described by a quantum wave function. Yet such superpositions are not seen in our consciously observed world, and the reason may have something to do with consciousness itself.

One longstanding view is that the act of conscious observation causes superposition to reduce, or collapse, to classical states, that consciousness causes collapse of the wave function. However, this view, termed the Copenhagen interpretation after the Danish origin of Neils Bohr, its early proponent, fails to consider the underlying reality of superposition, and puts consciousness outside science. But rather than consciousness causing collapse, as in the Copenhagen interpretation, Sir Roger Penrose has taken the opposite approach, suggesting that collapse causes consciousness (or *is* consciousness), a process in fundamental spacetime geometry, the fine scale structure of the universe, each OR event a qualia moment of subjective experience. Such events would be occurring ubiquitously in microscopic electrically charged environments throughout the universe, quickly reaching threshold and undergoing OR with random, meaningless, and disjointed protoconscious qualia. However, such primitive experiences could include pleasurable feelings or painful ones.

If so, OR events and qualia were occurring when life began, eg, in earth's primordial soup billions of years ago. Biomolecular self-organization could have been driven by optimizing pleasurable OR qualia, and avoiding painful ones. Were pleasurable qualia the spark of life driving evolution? Do they continue to be so?

In the early universe, and continuing to the present time, OR events would generally occur in electrically charged, polar environments like water or most forms of matter. There, quantum states quickly entangle and react chemically to reach OR threshold (decoherence), producing random, noncognitive protoconscious qualia which would come and go without a trace. However, also present in the early universe, eg, in the primordial soup from which life began, were nonpolar, uncharged oil-like environments of pi electron resonance clouds. When properly arrayed in nonpolar regions, pi electron resonance clouds are quantum-friendly, enabling superpositions to avoid random entanglements, and be orchestrated (Orch OR) in appropriate structural lattices with resonance, memory, and inputs. Orch OR events, eg, in microtubules inside brain neurons, could then culminate in meaningful, rich conscious moments.

Quantum friendly nonpolar regions pervade biology, buried within cores of microtubules and nearly all biomolecules, shielded from polar, aqueous interactions, and defined by a solubility parameter akin to olive oil. The Meyer–Overton correlation shows such nonpolar sites, eg, composed of aromatic amino acid pi electron resonance clouds in protein interiors, to be the sites where anesthetics act to selectively erase consciousness. The Meyer–Overton quantum underground appears to host consciousness in the brain, and may have enabled the origin of life.

It is suggested here that life originated billions of years ago to optimize OR-mediated qualia in nonpolar molecules in the primordial soup. Pi electron resonance clouds in dopamine-like amphipathic molecules coalesced in geometric pi-stacks, forming micelle-like proto-cells, RNA, membranes, and simple proteins with quantum-friendly regions for OR events. Positive pleasurable feelings, and avoidance of negative ones, are suggested to have provided feedback for self-organizing pi stack geometries optimal for pleasure. Absorption of ambient terahertz, gigahertz, and megahertz radiation help promote resonance, larger micelle structures, microtubules, cilia, centrioles, flagella, eukaryotic cells, and eventually the brain, in pursuit of feelings, resonating with the fine-scale structure of the universe.

ACKNOWLEDGMENTS

Thanks to Sir Roger Penrose, Jack Tuszynski, and Travis Craddock for collaboration; Paul Fini, Debra Knowles, and Dave Cantrell for artwork; and Marjan MacPhee, Kamber Geary, Nicolle Harbor, and Abi Behar-Montefiore for manuscript support.

REFERENCES

Albrecht-Buehler, G., 1992. Rudimentary form of cellular "vision". Proceedings of the National Academy of Sciences of the United States of America 89, 8288–8292.

Balestra, F.R., von Tobel, L., Gönczy, P., 2015. Paternally contributed centrioles exhibit exceptional persistence in *C. elegans* embryos. Cell Research 25, 642–644.

Barrow, J.D., Tipler, F.J., 1986. The Anthropic Cosmological Principal. Oxford University Press, Oxford.

Bell, G., 1982. The Masterpiece of Nature: The Evolution and Genetics of Sexuality. Croom Helm, London.

Benioff, P., 1982. Quantum mechanical Hamiltonian models of turing machines. Journal of Statistical Physics 29, 515–546.

Carter, B., 1974. Large number of coincidences and the anthropic principle in cosmology. In: IAU Symposium 63: Confrontation of Cosmological Theories with Observational Data. Reidel, Dordrecht, pp. 291–298. Republished in General Relativity and Gravitation (2011) 43(11):3225–3233.

Chalmers, D.J., 1996. The Conscious Mind – In Search of a Fundamental Theory. Oxford University Press, New York.

Churchland, P.S., 2013. Touching a Nerve – The Self as Brain. W.W. Norton & Company, New York.

Craddock, T., St George, M., Freedman, H., Barakat, K., Damaraju, S., Hameroff, S., Tuszynski, J.A., 2012a. Computational predictions of volatile anesthetic interactions with the microtubule cytoskeleton: implications for side effects of general anesthesia. PLoS One 7 (6), e37521. http://dx.doi.org/10.1371/journal.pone. 0037251.

Craddock, T., Tuszynski, J., Hameroff, S., 2012b. Cytoskeletal signaling: is memory encoded in microtubule lattices by CaMKII phosphorylation? PLoS Computational Biology 8 (3), e1002421. http://dx.doi.org/10.1371/journal.pcbi.1002421.

Craddock, T.J.A., Friesen, D., Mane, J., Hameroff, S., Tuszynski, J.A., 2014. The feasibility of coherent energy transfer in microtubules. Journal of the Royal Science Interface 11, 20140677.

Craddock, T.J.A., Hameroff, S.R., Tuszynski, J.A., 2015. Anesthetics act in quantum channels in brain microtubules to prevent consciousness. Current Topics in Medicinal Chemistry 15, 523−533.

Damasio, A., 1999. The Feeling of What Happens. Harcourt, San Diego.

Dawkins, R., 1986. The Blind Watchmaker. W.W. Norton & Company, New York.

Dawkins, R., 1989. The Selfish Gene. Oxford University Press, Oxford.

Dennett, D.C., 1991. Consciousness Explained. Little Brown, Boston.

Dennett, D.C., 1995. Darwin's Dangerous Idea: Evolution and the Meanings of Life. Simon and Schuster, New York.

Deutsch, D., 1985. Quantum theory, the Church − turing principal and the universal quantum computer. Proceedings of the Royal Society of London 400, 97−117.

Dixit, R., Ross, H., Goldman, Y.E., Holzbaur, E.L., February 22, 2008. Differential regulation of dynein and kinesin motor proteins by tau. Science 319 (5866), 1086−1089.

Emerson, D., Weiser, B., Psonis, J., Liao, Z., Taratula, O., Fiamengo, A., Wang, X., Sugasawa, K., Smith, A., Eckenhoff, R., Dmochowski, I., 2013. Direct modulation of microtubule stability contributes to anthracene general anesthesia. Journal of the American Chemical Society 135, 5398.

Engel, G., Calhoun, T., Read, E., Ahn, T., Caron Manc Caronal, T., Cheng, Y., Blankenship, R., Fleming, G., 2007. Evidence for wave-like energy transfer through quantum coherence in photosynthesis systems. Nature 446, 782−786.

Everett, H., 1957. Relative state formulation of quantum mechanics. Reviews of Modern Physics 29, 454.

Feynman, R.P., 1986. Quantum mechanical computers. Foundations of Physics 16, 507−531.

Freud, S., 1961. Beyond the Pleasure Principle. Trans. James Strachey, the standard ed. Liveright Publishing Corporation, New York.

Frohlich, J., 1968. Long range coherence and energy storage in biological systems. International Journal of Quantum Chemistry 2, 641−649.

Frohlich, H., 1970. Long range coherence and actions of enzymes. Nature 228, 1093.

Frohlich, H., 1975. The extraordinary dielectric properties of biological materials and the action of enzymes. Proceedings of the National Academy of Sciences of the United States of America 72, 4211−4215.

Garham, C.P., Vemu, A., Wilson-Kubalek, E.M., Yu, I., Szyk, A., Lander, G.C., Milligan, R.A., Roll-Mecak, A., May 21, 2015. Multivalent microtubule recognition by tubulin tyrosine ligase-like family glutamylases. Cell 161 (5), 1112−1123.

Hameroff, S.R., Penrose, R., 1996a. Orchestrated reduction of quantum coherence in brain microtubules: a model for consciousness. In: Hameroff, S.R., Kaszniak, A.Q., Scott, A.C. (Eds), Toward a science of consciousness; the first Tucson discussions and debates, MIT Press, Cambridge Mathematics and Computers in Simulation 40, 453−480.

Hameroff, S.R., Penrose, R., 1996b. Conscious events as orchestrated space-time selection. Journal of Consciousness Studies 1, 36−53.

Hameroff, S., Penrose, R., 2014a. Consciousness in the universe: a review of the 'Orch OR' theory. Physics of Life Reviews 11 (1), 39−79.

Hameroff, S., Penrose, R., 2014b. Reply to seven commentaries on "consciousness in the universe: review of the 'Orch OR' theory". Physics of Life Reviews 11 (1), 94−100.

Hameroff, S., Penrose, R., 2014c. Reply to criticism of the 'Orch OR qubit' − orchestrated objective reduction is scientifically justified. Physics of Life Reviews 11 (1), 104−112.

Hameroff, S., Watt, R.C., 1982. Information processing in microtubules. Journal of Theoretical Biology 98, 549−561.

Hameroff, S., 1987. Ultimate Computing-biomolecular Consciousness and Nanotechnology. Elsevier, Amsterdam.

Hameroff, S., 1998. Did consciousness cause the Cambrian evolutionary explosion? In: Hameroff, S.R., Kaszniak, A.W., Scott, A.C. (Eds.), Toward a Science of Consciousness II: The Second Tucson Discussion and Debates. MIT Press, Cambridge.

Hameroff, S., 2006. The entwined mysteries of anesthesia and consciousness. Anesthesiology 105, 400−412.

Hameroff, S., 2012. How quantum brain biology can rescue conscious free will. Frontiers in Integrative Neuroscience 6, 1−17.

Kauffman, S., 1993. The Origins of Order: Self Organization and Selection in Evolution. Oxford University Press, Oxford.

Koch, C., 2012. Consciousness: Confessions of a Romantic Reductionist. MIT Press, Cambridge.

Langton, C.G. (Ed.), 1995. Artificial Life: An Overview. MIT Press, Cambridge.

Libet, B., Wright Jr., E.W., Feinstein, B., Pearl, D.K., 1979. Subjective referral of the timing for a conscious sensory experience-a functional role for the somatosensory specific projection system in man. Brain 102, 193−224.

Margulis, L., Sagan, D., 1995. What Is Life? Simon Schuster, New York.

Meyer, H., 1901. Zur Theorie der Alkolnarkose. Naunyn-Schmiedeberg's Archives of Experimental Pathology and Pharmacology 46, 338−346.

Miller, S., Urey, H.C., 1959. Organic compound synthesis on the primitive earth. Science 130 (3370), 245−251.

Nagel, T., 1974. What us it like to be a bat? The Philosophical Review 83 (4), 435−450.

Nogales, E., Wolf, S.G., Downing, K.H., 1998. Structure of the tubulin dimer by electron crystallography. Nature 391, 199−203.

Ouyang, M., Awschalon, D.D., 2003. Coherent spin transfer between molecularly bridged quantum dots. Science 301, 1074−1078.

Overton, E., 1901. Studein ueber die narkosen. Verlag von Gustav Fischer, Switzerland.

Pan, J., Xo, J., Eckenhoff, M., Eckenhoff, R., 2007. Halothane binding proteome in human brain cortex. Journal of Proteome Research 6, 582−592.

Panksepp, J., 1998. Affective Neuroscience: The Foundations of Human and Animal Emotions. Oxford University Press, New York.

Peil, K.T., 2014. Emotion: the self-regulatory sense. Global Advances in Health and Medicine 2, 80−108.

Penrose, R., Hameroff, S.R., 1995. What gaps? reply to Grush and Churchland. Journal of Consciousness Studies 2, 98−112.

Penrose, R., 1989. The Emperor's New Mind: Concerning Computers, Minds, and the Laws of Physics. Oxford University Press, Oxford.

Penrose, R., 1994. Shadows of the Mind-a Search for the Missing Science of Consciousness. Oxford University Press, Oxford.

Penrose, R., 1996. On gravity's role in quantum state reduction. General Relativity and Gravitation 28, 581−600.

Pullman, B., Pullman, A., 1963. Quantum Biochemistry. Interscience, New York.

Rasmussen, S., Karampurwala, H., Vaidyaath, R., Jensen, K., Hameroff, S., 1990. Computational connectionism within neurons: a model of cytoskeletal automata subserving neural networks. Physica D: Nonlinear Phenomena 42, 428–449.

Rasmussen, S., 2010. Life after the synthetic cell. Nature 465 (7297), 422.

Ridley, M., 2008. The Cooperative Gene. Simon and Schuster, New York.

Sahu, S., Ghosh, S., Hirata, K., Fujita, D., Bandyopadhyah, A., 2013a. Multi-level memory-switching properties of a single brain microtubule. Applied Physics Letters 102, 123701.

Sahu, S., Ghosh, S., Fujita, D., Bandyopdhyay, A., 2014. Live visualizations of single isolated tubulin protein self-assembly via tunneling current: effect of electromagnetic pumping during spontaneous growth of microtubule. Scientific Reports 4, 7303.

Sahu, S., Ghosh, S., Ghosh, B., Aswanid, K., Hirata, K., Fujita, D., Bandyopadhyay, A., 2013b. Atomic water channel controlling remarkable properties of a single brain microtubule: correlating single protein to its supramolecular assembly. Biosensors and Bioelectronics 47, 141–148.

Schrödinger, E., 1935. Die gegenwarte situation in der quantenmechanik. Naturwissenschaften 23, 807–812, 823–828, 844–849. Translation by Trimmer,.T. In: Proceedings of the American Philosophical Society 124, 323–338.

Sherrington, C.S., 1951. Man on His Nature. Cambridge University Press, Cambridge.

Shimony, A., 1993. Search for a Naturalistic World View, Vol. II Natural Science and Metaphysics. Cambridge University Press, Cambridge.

Smith, S., Watt, R., Hameroff, S., 1984. Cellular automata in cytoskeletal lattice protients. Physica D: Nonlinear Phenomena 10, 168–174.

Stapp, H.P., 2007. Mindful Universe: Quantum Mechanics and the Participating Observer. Springer, New York.

Szent-Gyorgyi, A., 1960. Introduction to a Submolecular Biology. Academic Press, Cambridge (Reprinted by Elsevier, 2012).

Tamulis, A., Grigalavicius, M., 2014. Quantum emtanglement in photoactive prebiotic systems. Systems and Synthetic Biology 8 (2), 117–140.

Tononi, G., 2012. Phi: A Voyage from the Brain to the Soul. Pantheon Books, New York.

Vattay, G., Salahub, D., Casbai, I., Nassimi, A., Kaufmann, S.A., 2015. Quantum criticality at the origin of life. Journal of Physics: Conference Series. http://dx.doi.org/10.1088/1742-6596/626/1/012023.

Whitehead, A.N., 1929. Process and Reality. Macmillan, New York.

Whitehead, A.N., 1933. Adventures of Ideas. Macmillan, London.

Chapter 21

Empathy, Theory of Mind, Cognition, Morality, and Altruism

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INTRODUCTION

Many researchers, as well as the general population, feel that empathy is the primary underlying motivator of altruistic behavior (Batson, 2009, 2012; De Waal, 2009; Rameson et al., 2012; Rifkin, 2009). This "weighted toward empathy" approach has an important impact on society—training programs to help teach altruistic attitudes to youngsters and adolescents, for example, often emphasize the empathic components of altruism and show little concern for other emotional issues in altruistic behavior and the importance of cognition (Oakley, 2014).

An important point of this chapter is that cognition plays a major role in altruistic behavior, as do emotions other than empathy. Empathy, in fact, can play a lesser role in altruism than is often acknowledged (Bernhardt and Singer, 2012; Decety and Yoder, 2015; Prinz, 2011). As Prinz notes, empathy is not only *not* necessary for altruistic actions—sometimes, it can actually get in the way of those actions. And empathy does not necessarily motivate altruism—Prinz notes, "one might judge that it is bad to kill an innocent person even if his vital organs could be used to save five others who desperately need transplants. Here, arguably, we feel cumulatively more empathy for the five people in need than for the one healthy person, but our moral judgment does not track that empathetic response." Other emotions besides empathy also play an important role in altruism, including feelings of disapprobation, disgust, contempt, gratitude, admiration, and guilt (Prinz, 2011).

Empathy can provide simplistic immediate assistance for others, but as with the cheating student who pleads for empathy, asking to be let off the hook "just this one time," sometimes knee-jerk empathetic responses to others' problems can create new problems, both for the person involved and for society as a whole. As Decety and Cowell note, "care-based morality piggybacks on older evolutionary motivational mechanisms associated with parental care. This explains why 'empathy' is not always the royal road to morality and can at times be a source of immoral action by favoring self- or kin-related interest" (Decety and Cowell, 2014).

As this chapter describes, sometimes empathic programmatic approaches to providing altruistic support for others can backfire, worsening the very situations they were meant to solve. Unfortunately, as discussed in detail further on, the all-too-human tendencies in these cases has long been to resist factual revelations about the failure of such programs and to instead redouble empathic efforts rather than to stand back and see whether very different approaches might serve populations in better stead.

Such empathy-heavy approaches can also contribute to a worsening of the divide between political parties. Those who don't support sometimes overly simplistic, empathic approaches to helping others, particularly the disadvantaged, can be easily demonized as heartless or racist. Little concern is given for the fact that truly compassionate ways of interacting with and helping others generally involve far more than simple empathy or obvious (and often subtly or not-so-subtly self-serving) demonstrations of helping (Fig. 21.1).

The focus of this chapter is to grapple with our knowledge of *empathy* and *theory of mind* (ToM), relate these concepts to the concept of *cognition*, and then synthesize these concepts in a nuanced fashion regarding their relationship to the overarching concept of *altruism*. This chapter forms an attempt to integrate strands of neuroscientific, psychological,

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00021-1

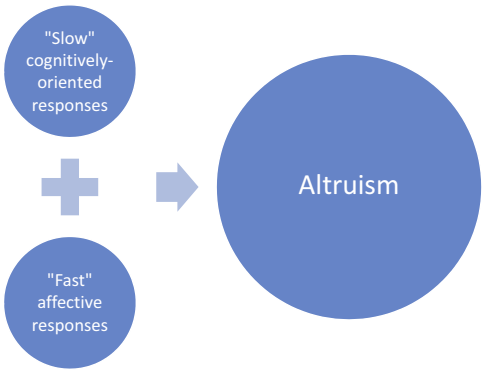

FIGURE 21.1 Altruism is often erroneously considered to be arising in large part from affective systems related to empathy. In reality, true altruism often involves both *fast* and *slow* processes in the Kahneman (2011) sense. In other words, altruism often involves "faster" affective (emotional) considerations, which include a much broader array of emotions than simple empathy and can include cortical as well as mesolimbic structures. But altruistic acts also include "slower" cognitive processes primarily affiliated with the orbitofrontal and prefrontal cortices. Helpful behavior, in fact, often involves a careful weighing of both affective and cognitive concerns. What seems at first helpful can, in the long run, prove harmful. Moreover, altruism is often thought of as something so obvious that it's hardly necessary to explain the term. Yet different groups can differ substantially in what they think is altruistic. A simple example of this phenomenon can be seen when examining the history of the Greek credit crisis from either a Northern or Southern European perspective.

and societal research to better understand how to truly help others (Fan et al., 2011).

It is enlightening to realize that three of the terms in the title of this chapter, empathy, ToM, and altruism, are neologisms, recently introduced into English, sometimes with underlying ideological agendas they support.[1] As neologisms, we should not expect these terms to correspond neatly with observable, measurable natural phenomena—that is, with nature "carved at the joints" (Campbell et al., 2011).

NEUROSCIENCE AND DYNAMICS OF EMPATHY

Empathy has received extravagant attention in the research literature—neuroscientific examples include (Bernhardt and Singer, 2012; Decety, 2015; Mathur et al., 2010; Walter, 2012; Zaki and Ochsner, 2012). To capture the fact that empathy often seems to include both affective and cognitive components, it is sometimes defined along the lines of (Zaki and Ochsner, 2012), who group the processes of empathy into three broad classes: "(1) experience sharing: vicariously sharing targets' internal states (Gallese et al., 2004), (2) mentalizing: explicitly considering (and perhaps understanding) targets' states and their sources (Leslie et al., 2004), and (3) prosocial concern: expressing motivation to improve targets' experiences (for example, by reducing their suffering) (Batson, 2011)." Along the lines of (3), however, it should be noted that a meta-analysis has shown only a weak correlation between empathy and prosocial behavior (Neuberg et al., 1997).

A number of studies have used functional MRI to identify brain regions involved in empathic response (see reviews by (Bernhardt and Singer, 2012; Decety, 2015; Fan et al., 2011; Shamay-Tsoory, 2010)). Not all studies find consistent regions, but many studies find involvement of the anterior cingulate gyrus, and to a lesser extent the ventromedial prefrontal cortex (vmPFC) and anterior insula. The anterior cingulate, together with posterior cingulate, is activated when the subject is in pain. Thus there may be a kind of mirroring function for pain, as there seems to be in premotor cortex for movements, although the cingulate is not among the regions identified as containing mirror neurons. The anterior insular is often responsive to interoceptive feeling, although no mirror functions have been reported for it. The vmPFC is often activated in moral judgments and when thinking about close relationships; it is also reported in ToM tasks. Thus the activation of vmPFC may be a more reflective aspect of empathy.

Fan and Han (2008) first used electroencephalography (EEG) to study the rapid evolution of a subject's response to pictures of others in pain. They distinguished an early and a later component of the empathy response. The early response occurred at 150−200 ms and was largely over the frontal aspects of the prefrontal cortex (PFC). The later response occurred at 400−600 m and seemed to be coming largely from medial areas; given the geometry of the regions they interpreted these later currents as reflecting activity in cingulate or medial PFC. They suggested that the first component reflected an immediate emotional response and the later response reflected more cognitive processing, and such an interpretation is often given. Nevertheless, while such an interpretation appeals to conventional wisdom, it does seem inconsistent with the usual attributions of cognitive functions to anterior PFC, and of emotional functions to the cingulate (sometimes called the limbic lobe).

Cheng et al. (2014) found that these two EEG components of the empathy response follow different time

1. *Empathy* is an English translation of the German word *Einfühlung*, literally "feeling into" another person's experience, particularly pain or distress. *Einfühlung* was coined by Robert Vischer in the mid 1800s (Vischer et al., 1993). In 1909, psychologist Edward Titchener (1909/2014) coined the English word *empathy* as a translation of *Einfühlung*. The phrase *theory of mind* was introduced by Premack and Woodruff (1978) in an article about chimpanzees being able to infer goals of an actor in a video. The term *altruism* (in French, *altruisme*), is the oldest of the neologisms, and was introduced by Auguste Comte (1798−1857), to oppose the term *egoism*, as part of a broad positivist program to reform human society and morals (Wilson, 2015, p. 90; Zaki and Ochsner, 2012).

courses during child development. Specifically the first component decreases in size during middle childhood, while the second seems to increase. Following the interpretation of others, they propose that the decrease in the first component reflects a decrease in emotional response and an increase in cognitive response with maturity. As pointed out earlier, an interpretation of the data consistent with the usual attributions of function, would be almost the reverse. Perhaps the initial shock value of others' pain decreases, while the "feeling with" in the anterior cingulate increases as children learn to imagine others' experiences. This interpretation is also consistent with the evidence on individual differences, discussed next. A related study finds that the later component, but not the earlier component, is predictive of actual generosity in behavior (Cowell and Decety, 2015).

Individual differences in empathy are evident to us in daily life. Furthermore, there has been much discussion about how empathy differs among autistic and psychopathic individuals. Some early fMRI studies of individual differences found rough correlations between activation of the cingulate cortex and questionnaire-based measures of empathic traits. Several EEG studies from Jean Decety's lab and collaborators have investigated how empathic response differs among autistic and psychopathic people; it turns out that although both groups are often said to exhibit diminished empathy, the brain responses of these two groups differ from normal in opposite ways. The psychopaths typically showed the same level of early response, but showed a diminished later component compared to normal subjects (Decety et al., 2015). In contrast, autistic individuals showed a higher early component (Fan et al., 2013).

Decety and his group also observed in psychopaths a greater decrease of mu rhythm (a kind of resting rhythm) over motor areas; such decrease is often associated with "mirror neuron" processing. This suggests that psychopaths may be simulating the actions of others, perhaps even more than normal subjects.

There is considerable variation between people in empathy. Some of this variation may be genetic. A genome-wide study confirmed an association between different variants of the oxytocin receptor and empathy's opposite, psychopathy, and also found other genetic associations (Bakermans-Kranenburg and van IJzendoorn, 2014).

THEORY OF MIND (ToM)

ToM also now termed "mentalizing," refers broadly to attributions of knowledge and intent to others. ToM has become a very popular area of study in social psychology in the past two decades. Nevertheless, even basic definitions remain contentious. In the original formulation of Premack and Woodruff (1978) it referred to inferring goals from actions: a chimpanzee was shown a series of pictures of a human actor attempting to accomplish something, and then asked to select one of two pictures of an outcome (presumably desired). The chimpanzee could do this fairly well. So, the phrase ToM originally referred to inferring others' goals—and by extension, to intentions.

The term was expanded during the 1990s to understanding the state of knowledge of actors, especially their false beliefs. More recently psychologists have studied the ability to correctly recognize emotions from others' faces (Ickes, 1993, 2001). It is not clear whether all these diverse aptitudes reflect a common underlying core competence; or, if not depending on a common core competence, in what ways, and to what extent these capacities enhance each other. What is clear is that the capacities described as "empathic accuracy" are, contrary to the expectations of many researchers in the 1990s, uncorrelated with the more usual (emotional) senses of the word empathy, across normal subjects as well as autistic individuals (Demurie et al., 2011; Zaki et al., 2008, 2009a,b). Interestingly, one recent study found a relationship between an oxytocin receptor gene, ToM, and prosocial behavior in children (Wu and Su, 2015), suggesting some genetic contribution to individual differences in emotional empathy.

THE RELATIONSHIP BETWEEN EMPATHY, ToM, MORALITY, AND OTHER NEURAL NETWORKS

Although both empathy and ToM are ill-defined, fMRI experiments that try to elicit various kinds of empathy usually activate several regions including the vmPFC (Fan et al., 2011), which is also an area that is elicited by many experiments that try to elicit various kinds of ToM functions (Siegal and Varley, 2002). There is little consensus on a concise characterization of the function of vmPFC. However we speculate, following (Siegal and Varley, 2002), that vmPFC may be where cognition meets emotion: that understanding of other people may allow a more effective altruism than simply an emotional response.

One interesting study related ToM, empathy, and the broad-scale mind-wandering to moral cognition (Bzdok et al., 2012, 2015). They note: "the neural network subserving moral decisions probably reflects functional integration of distributed heterogeneous networks, is dissociable into cognitive and affective components, as well as highly similar to the brain's default activity pattern." Through meta-analysis Bzdok's team revealed that ToM appears to involve a distinct abstract−inferential social−cognitive network involving the dorsomedial PFC, frontal pole, inferior frontal gyrus, middle temporal gyrus, medial PFC, precuneus, temporal pole, temporoparietal junction, and vmPFC. This network appears to overlap significantly with the brain activity patterns observed during moral cognition.

By contrast, as Bzdok's group went on to reveal, empathy appears to activate a distinct automatic—emotional social—cognitive network that "vicariously maps others' affective states." The network includes the anterior cingulate cortex, anterior insula, amygdala, brainstem, dorsomedial PFC, inferior frontal gyrus, middle temporal gyrus, posterior cingulate cortex, supplementary motor area, and the temporoparietal junction. The study's conclusion was that the neural correlates of moral cognition more strongly resemble ToM than they do empathy.

THE MESOLIMBIC AND CORTICAL SYSTEMS AND THEIR RELATIONSHIP WITH ALTRUISM

Research has revealed that humans feel pleasure at the altruistic act of giving because it activates their mesolimbic "pleasure" system, which stimulates activation of dopamine. As noted in (Moll et al., 2006), "donating to societal causes recruited two types of reward systems: the VTA—striatum mesolimbic network, which also was involved in pure monetary rewards, and the subgenual area, which was specific for donations and plays key roles in social attachment and affiliative reward mechanisms in humans… and other animals." This mesolimbic activation, it seems, is the source of that "warm glow" we get when we help others. (As Sam Kean memorably puts it: "What your mother told you, then, is true: it is better to give than to receive. She probably just didn't realize that, neurologically, giving is roughly on par with eating fudge or getting laid" (Kean, 2015).) Warm mesolimbic "glow" feelings are also related to the glow of drug addiction—in other words, these feelings may be helpful at times, but they are not an unalloyed good.

A well-known study on pathological generosity (Ferreira-Garcia et al., 2013; Kean, 2015), revealed that damage to the lenticular nucleus and nearby pathways induce an overly generous attitude that can cause difficulties in a person's being able to function in society. This appears to happen because the lenticular nucleus and nearby pathways serve as a conduit to feed information about what is happening in the mesolimbic system back toward the frontal cortices. This severing of the feedback loop can induce a person to give incessantly for that hit of dopamine pleasure, in a somewhat analogous fashion to rats who will, in preference to receiving food or water, die of exhaustion from repeatedly pressing a lever to activate metal electrodes implanted into their nucleus accumbens (Hoult, 1984).

In Ferreira-Garcia et al.'s case of pathological generosity, "Mr. A." suffered a left lenticulocapsular stroke that changed his personality from that of a cautious and responsible individual to a person who was financially incapable of managing his affairs. As (Ferreira-Garcia et al., 2013) note:

> *[Mr. A.] would spend his money with street kids, buying them soda, candies, and junk food. There was no evidence of pedophilia, as emphasized by his wife, brother-in-law, and friends, who were always with him when he was out. Were it not for the close attention of Mr. A's wife, he would be constantly in debt. At one point, Mr. A and his brother-in-law started a small business of homemade fries, which eventually failed because he did not worry about debtors and because he gave away most of his product. If confronted by his mother or wife, he would make a joke and evade discussion. If pressed further, he sometimes would become angry and then leave the house for a while.*

This unusual case clarifies that tempering mechanisms that can judiciously tone down the activation of mesolimbic areas—in other words, mechanisms that can help douse the "warm glow"—appear to be provided, at least in part, by the PFC and orbitofrontal cortices, as well as by the disinhibiting desired actions and inhibiting undesired actions decision making that occurs in the basal ganglia. The prefrontal cortex and orbitofrontal cortices, in fact, appear to be generally involved in the decisions underlying "real-life altruistic behaviors" (Moll et al., 2005, 2006). It appears the lateral orbitofrontal cortex restricts the impulse to give through aversive mechanisms such as anger, moral disgust, and other "more abstract forms of culturally mediated social disapproval" (Moll et al., 2006). General decision making encompasses a broad swathe of neural circuitry (Hikosaka et al., 2014; Hwang, 2013; Lee, 2013).

A number of different medical and nonmedical conditions can contribute to an overwillingness to help others, to the point where the "giver" can him or herself become endangered, and the subject of the givers' attention can be harmed (Oakley et al., 2012; Oakley, 2013). Such conditions include Williams syndrome (Riby et al., 2012), dementia (Dorey et al., 2008; Mendez et al., 2006), neurosyphilis (Nágera, 1944), Parkinson's disease treated with dopaminergic drugs (O'Sullivan et al., 2010), and the amorphous behavior affiliated with "codependency" (McGrath and Oakley, 2012).

WHAT IS ALTRUISM? (HINT: IT'S NOT NECESSARILY WHAT IT LOOKS LIKE)

Jacob Neusner and Bruce Chilton (2005) supplied an expanded definition of altruism in their *Altruism in World Religions* (p. xi):

> *A standard dictionary definition describes altruism as "unselfish concern for the welfare of others: opposed to egoism." The four components of this definition distinguish altruism from other kinds of care for others. "Unselfish"*

carries with it the notion that the altruist acts for the sake of the other rather than himself or herself. "Concern" suggests that altruism entails a motivation as well as an action. "Welfare" means that the goal is to benefit, rather than harm, the other. And "others" implies that the altruist is capable of seeing the object of concern as someone distinct from himself or herself.

Altruistic behavior is often thought to be virtually synonymous with prosocial behavior, which is the subject of an immense body of research in the social sciences (Beilin and Eisenberg, 2013; Bénabou and Tirole, 2005; Dovidio et al., 2006; Schroeder and Graziano, 2015). But in fact, surprisingly often, truly altruistic behavior can seem superficially as antisocial rather than prosocial (Oakley, 2013).

THE PROBLEM WITH PROSOCIALITY

We should point out that there is confusing and circular reasoning going on in any attempt to define prosocial behavior. It is useful to take a look at the popular description from Wikipedia:

Prosocial behavior, or "voluntary behavior intended to benefit another," (Eisenberg et al., 2007) is a social behavior that "benefit[s] other people or society as a whole," (Psychwiki.com) "such as helping, sharing, donating, co-operating, and volunteering" (Brief and Motowidlo, 1986). These actions may be motivated by empathy and by concern about the welfare and rights of others, (Sanstock, 2007, pp. 489–491) as well as for egoistic or practical concerns (Eisenberg et al., 2007). Evidence suggests that prosociality is central to the well-being of social groups across a range of scales (Helliwell and Putnam, 2004; Straubhaar et al., 2013). Empathy is a strong motive in eliciting prosocial behavior, and has deep evolutionary roots (Decety, 2011).

Using this description of prosociality, such behaviors as stepping back to allow a person to learn self-efficacy; or turning off empathy and refusing to give to an alcoholic begging for money for a bottle of whisky on a street corner—or for that matter, refusing to give an undeserved bump in grade to a beseeching student—would tend to not be counted as prosocial behavior, even though such behavior could be motivated by concern for the welfare of others. In a similar way, proponents of the death penalty can point toward solid scientific research indicating that the death penalty spares between 10 and 24 innocent victims of murder (Sunstein and Vermeule, 2005)—yet those who support the death penalty are rarely accused of being prosocial.

For the purposes of this chapter, prosocial behavior is taken with its usual connotation of being superficially helpful for others, whether or not it is truly helpful in the greater scheme, either for that person or for society. Altruistic behavior, on the other hand is taken to mean that the behavior is indeed truly helpful for the person in the long run, or for society as a whole. Pathologically altruistic behavior is behavior that is intended to be altruistic, but which does not truly result in overall altruistic outcomes (Oakley, 2013).

HARMFUL PROSOCIAL BEHAVIOR

By way of background, it's important to note that in many areas, scientific research can, even with researchers' best intentions, simply reify previous findings—to the detriment of scientific progress (Hyman, 2010). Thus, it's no surprise to find that much scientific research supports the commonsense notion that prosocial behavior is essentially altruistic—or indeed, that superficially prosocial activities are truly prosocial in the sense of denoting behavior that is positive and helpful for others. Who would even conceive of conducting research that might reveal that prosocial behavior might not be altruistic?

But occasional glimmers reveal that prosocial behavior is not necessarily altruistic.

An intriguing study was conducted by the influential American criminologist Joan McCord (1978).[2] This was related to a previous intervention that was conducted in the late 1930s and early 1940s. In this program, approximately 500 Boston school boys were randomly assigned to two different groups—one group was the control group, and received no intervention. The other group was assigned to a five year treatment program that included counselors who visited the families, on average, twice each month; the families were encouraged to call on the program for assistance. Many of these "intervention" students also received academic tutoring, some received medical or psychiatric attention, were sent to summer camps, and were brought into contact with community programs such as the Boy Scouts and the YMCA.

2. Joan McCord was well-known for her ability to marshal "mountains of evidence to question the effectiveness of social programs championed by both liberals and conservatives" (Martin, 2004). McCord found that officials took sometimes affront to the idea of evaluation of social programs, since if one was found ineffective, it could tar other social programs. Her response was to note "That fear, perhaps justified in some quarters, would be like blocking publication of damaging effects of Celebrex, thalidomide, or estrogen because the publication could slow work in disease prevention" (Martin, 2004). Other important works which McCord (1979) helped author include (Dishion et al., 1999), which explored developmental and intervention evidence relevant to iatrogenic effects in peer-group interventions, and pointed toward the surprising relationship between maternal self-confidence and maternal affection, along with father's deviance, parental aggressiveness, parental conflict, and supervision, in accounting for a significant proportion of the variance in number of convictions for serious crimes.

Thirty years later, Joan McCord was able to track down 480 of the original 506 participants in the study. Forty-eight had died. Questionnaires were sent to 208 men in the treatment group and 202 from the control group. Responses were received from 113 men in the treatment group (54%) and 122 men in the control group (60%). Subjectively, members of the treatment group gave it high marks.

However, as McCord notes:

> *Despite the large number of comparisons between treatment and control groups, none of the objective measures confirmed hopes that treatment had improved the lives of those in the treatment group. The objective evidence presents a disturbing picture. The program seems not only to have failed to prevent its clients from committing crimes—thus corroborating studies of other projects… but also to have produced negative side effects. As compared with the control group,*

1. Men who had been in the treatment program were more likely to commit (at least) a second crime.
2. Men who had been in the treatment program were more likely to evidence signs of alcoholism.
3. Men from the treatment group more commonly manifested signs of serious mental illness.
4. Among men who had died, those from the treatment group died younger.
5. Men from the treatment group were more likely to report having had at least one stress-related disease; in particular, they were more likely to have experienced high blood pressure or heart trouble.
6. Men from the treatment group tended to have occupations with lower prestige.
7. Men from the treatment group tended more often to report their work as not satisfying.

McCord suggested several explanations for her findings.

1. Interaction with "hard-core" unemployables "may produce later internal conflicts that manifest themselves in disease and/or dissatisfaction."
2. "Agency intervention may create dependency upon outside assistance. When this assistance is no longer available, the individual may experience symptoms of dependency and resentment. The treatment program may have generated such high expectations that subsequent experiences tended to produce symptoms of deprivation."
3. "[T]hrough receiving the services of a 'welfare project,' those in the treatment program may have justified the help they received by perceiving themselves as requiring help."

Joan McCord is not alone in finding substantive problems with well-meaning research projects that are not accorded the same scientific scrutiny as less obviously well-intentioned programs. For examples involving the elimination of racial prejudice, the reduction of sex differences in mathematical performance, the reduction of drug use and adolescent behavior problems, the mitigation of posttraumatic stress disorder, and the reduction of family violence, among many other areas, see (Cole, 2001; Eidelson and Soldz, 2012; Kalev et al., 2006; Lilienfeld, 2007; Petrosino et al., 2000, 2003; Sander and Taylor, 2012; Wilson, 2011; Wright and Cummings, 2005).

ALTRUISM THROUGH EVOLUTION TO TODAY

How did our species become (partly) altruistic? Most explanations for the evolution of altruism (or of cooperation—not entirely the same) run into the "free-rider" problem (related to the problem framed as "The Prisoner's Dilemma"). Briefly stated, this is that although if everyone cooperates, we are all better off, it is generally thought that the individual has a better chance of success if she or he does not cooperate but enlists the help of altruists without returning the favor. Since selective pressures on genes act on individuals rather than for groups, this scenario argues against genes predisposing to altruistic behaviors becoming common (Wilson, 2015).

Various forms of altruism have repeatedly evolved, of which the best known are social insects. The most commonly accepted idea to explain the evolution of altruism or cooperation is kin selection, or "inclusive fitness." This means that helping those with whom you share a large fraction of your genes propagates those genes. Thus altruism can arise when nest-mates share a large fraction of their genes as often happens among the well-known social insects (eg, sister wasps share three-fourths of their genes).

This scenario has been challenged by several eminent theoreticians and biologists (eg, Nowak et al., 2010; see also the extensive correspondence on this paper), who argue kin selection can only explain altruism under very specific unusual conditions, which rarely hold in nature, but that under some more commonly observed conditions on population structure, altruism emerges as a winning strategy. These ideas are related to the other popular explanation of altruism, that is reciprocity, popularized by Robert Wright (1994). There is still some controversy about this, and it seems to run into trouble in human evolution, where altruism is far from perfect (André and Day, 2007). Some have suggested some mix of kin selection and reciprocity may allow imperfect reciprocity to be selected (Ale et al., 2013).

This is not the place to definitively answer this question, but we point out two approaches that draw on the unique

social structure of human ancestors. First, models and behavioral-economic analyses have shown that altruistic tendencies can be selected (Choi and Bowles, 2007):

1. If people who in cooperative bands do significantly better than those in noncooperative groups;
2. If people are somewhat rational—selecting bands that are more cooperative, if they can get in;
3. If people can move somewhat freely between groups.

Anthropologists' long-time observations and quantitative data on preferences for cooperators among the Hadza (Apicella et al., 2012) confirm some of the essential characteristics of these models in hunter-gatherer societies, which are thought to resemble our ancestral human societies for 3 million years.

A second hypothesis by Sarah Hrdy derives from the need for wide-ranging foraging and cooperative hunting necessary for the lifestyle that human ancestors adopted about 4−5 Ma on the savannah. Plant food comes in rare and hidden packages; hunting animals requires skilled tracking and stalking. For both food types, humans had to forage far from camp and could not easily take young children. Looking after other people's children (as Hrdy calls it, "alloparenting") seems to be widespread among hunter-gatherer groups today and most likely is an ancestral practice that was crucial for survival on the savannah. Hrdy argues that generalized empathy would be necessary for such practices.

She notes (Hrdy, 2009, p. 66): "rearing conditions among a line of early hominins meant that youngsters grew up depending on a wider range of caretakers than just their mothers, and this dependence produced selection pressures that favored individuals who were better at decoding the mental states of others, and figuring out who would help and who would hurt."

Since hunter-gatherer bands are often composed of unrelated extended families (Dyble et al., 2015), it could be that both kin selection and reciprocity played roles in enabling alloparenting.

How do these considerations shed light on the role of empathy in the evolution of human altruism?

Empathy may be a component of much altruistic behavior, but other feelings besides empathy, such as loyalty, obligation, and even guilt, also contribute to cooperative or altruistic behavior. As (Lee, 1984) points out, the most common topic of conversation among his hunter-gatherer subjects was whether particular people had fulfilled their traditional obligations. So perhaps empathy was not the only or even the main driver of human altruism. Nevertheless, empathy has helped shape human altruism, and may have shaped other crucial aspects of human evolution, such as culture.

We have a very long childhood and require children to learn a complex culture. Numerous studies have documented that we learn complex series of arbitrary actions faster than our primate relatives (Dean et al., 2012), and that social interaction is the key.

However, in the end, we must acknowledge that altruism in today's complex, large-scale environment, where millions of people interact through a number of widely varying systems, including both government, business, and religious enterprises, is nothing like the evolutionary "savannah style" simplicity of past human environments, where perhaps 150 people were the most that a person would interact with (Dunbar, 1992). As a consequence, it is important to be aware of the extraordinary complexity that underlies our attempts to both help and hurt one another, and to be wary of approaches that place undue emphasis on any particular neuroscientific underpinning related to morality and altruism.

REFERENCES

Ale, S.B., Brown, J.S., Sullivan, A.T., 2013. Evolution of cooperation: combining kin selection and reciprocal altruism into matrix games with social dilemmas. PLoS One 8 (5), e63761.

André, J.-B., Day, T., 2007. Perfect reciprocity is the only evolutionarily stable strategy in the continuous iterated prisoner's dilemma. Journal of Theoretical Biology 247 (1), 11−22.

Apicella, C.L., Marlowe, F.W., Fowler, J.H., Christakis, N.A., 2012. Social networks and cooperation in hunter-gatherers. Nature 481 (7382), 497−501.

Bakermans-Kranenburg, M.J., van IJzendoorn, M.H., 2014. A sociability gene? Meta-analysis of oxytocin receptor genotype effects in humans. Psychiatric Genetics 24 (2), 45−51.

Batson, C.D., 2009. Empathy-induced altruistic motivation. In: Mikulincer, M., Shaver, P.R. (Eds.), Prosocial Motives, Emotions, and Behavior. American Psychological Association, Washington, DC, pp. 15−34.

Batson, C., 2011. Altruism in Humans. Oxford University Press.

Batson, C.D., 2012. The empathy-altruism hypothesis. In: Decety, J. (Ed.), Empathy: From Bench to Bedside. MIT Press, Cambridge, MA, pp. 41−54.

Beilin, H., Eisenberg, N., 2013. The Development of Prosocial Behavior. Academic Press.

Bénabou, R., Tirole, J., 2005. Incentives and Prosocial Behavior. National Bureau of Economic Research.

Bernhardt, B.C., Singer, T., 2012. The neural basis of empathy. Annual Review of Neuroscience 35, 1−23.

Brief, A.P., Motowidlo, S.J., 1986. Prosocial organizational behaviors. Academy of Management Review 11 (4), 710−725.

Bzdok, D., Schilbach, L., Vogeley, K., Schneider, K., Laird, A.R., Langner, R., Eickhoff, S.B., 2012. Parsing the neural correlates of moral cognition: ALE meta-analysis on morality, theory of mind, and empathy. Brain Structure and Function 217 (4), 783−796.

Bzdok, D., Groß, D., Eickhoff, S.B., 2015. The neurobiology of moral cognition: relation to theory of mind, empathy, and mind-wandering. In: Handbook of Neuroethics. Springer, pp. 127−148.

Campbell, J.K., O'Rourke, M., Slater, M.H., 2011. Carving Nature at Its Joints: Natural Kinds in Metaphysics and Science. MIT Press, Cambridge, MA.

Cheng, Y., Chen, C., Decety, J., 2014. An EEG/ERP investigation of the development of empathy in early and middle childhood. Developmental Cognitive Neuroscience 10, 160–169.

Choi, J.K., Bowles, S., 2007. The coevolution of parochial altruism and war. Science 318 (5850), 636–640. http://dx.doi.org/10.1126/science.1144237.

Cole, S., 2001. What's Wrong With Sociology? Transaction Publishers, New Brunswick, NJ.

Cowell, J.M., Decety, J., 2015. The neuroscience of implicit moral evaluation and its relation to generosity in early childhood. Current Biology 25 (1), 93–97.

De Waal, F.B.M., 2009. The Age of Empathy. Crown, New York, NY.

Dean, L.G., Kendal, R.L., Schapiro, S.J., Thierry, B., Laland, K.N., 2012. Identification of the social and cognitive processes underlying human cumulative culture. Science 335 (6072), 1114–1118.

Decety, J., Cowell, J.M., 2014. The complex relation between morality and empathy. Trends in Cognitive Sciences 18 (7), 337–339. http://dx.doi.org/10.1016/j.tics.2014.04.008.

Decety, J., Yoder, K.J., 2015. Empathy and motivation for justice: cognitive empathy and concern, but not emotional empathy, predict sensitivity to injustice for others. Social Neuroscience 1–14. http://dx.doi.org/10.1080/17470919.2015.1029593.

Decety, J., Lewis, K.L., Cowell, J.M., 2015. Specific electrophysiological components disentangle affective sharing and empathic concern in psychopathy. Journal of Neurophysiology. http://dx.doi.org/10.1152/jn.00253.2015.

Decety, J., 2011. The neuroevolution of empathy. Annals of the New York Academy of Sciences 1231, 35–45. http://dx.doi.org/10.1111/j.1749-6632.2011.06027.x.

Decety, J., 2015. The neural pathways, development and functions of empathy. Current Opinion in Behavioral Sciences 3, 1–6. http://dx.doi.org/10.1016/j.cobeha.2014.12.001.

Demurie, E., De Corel, M., Roeyers, H., 2011. Empathic accuracy in adolescents with autism spectrum disorders and adolescents with attention-deficit/hyperactivity disorder. Research in Autism Spectrum Disorders 5 (1), 126–134.

Dishion, T.J., McCord, J., Poulin, F., 1999. When interventions harm: peer groups and problem behavior. American Psychologist 54 (9), 755.

Dorey, J.-M., Beauchet, O., Anterion, C.T., Rouch, I., Krolak-Salmon, P., Gaucher, J., Gonthier, R., Akiskal, H.S., 2008. Behavioral and psychological symptoms of dementia and bipolar spectrum disorders: review of the evidence of a relationship and treatment implications. CNS Spectrums 13 (09), 796–803.

Dovidio, J.F., Piliavin, J.A., Schroeder, D.A., Penner, L., 2006. The Social Psychology of Prosocial Behavior. Lawrence Erlbaum Associates Publishers.

Dunbar, R.I., 1992. Neocortex size as a constraint on group size in primates. Journal of Human Evolution 22 (6), 469–493.

Dyble, M., Salali, G., Chaudhary, N., Page, A., Smith, D., Thompson, J., Vinicius, L., Mace, R., Migliano, A., 2015. Sex equality can explain the unique social structure of hunter-gatherer bands. Science 348 (6236), 796–798.

Eidelson, R., Soldz, S., May, 2012. Does Comprehensive Soldier Fitness Work: CSF Research Fails the Test. Working Paper Number 1. Coalition for an Ethical Psychology, Bala Cynwyd, PA.

Eisenberg, N., Fabes, R.A., Spinrad, T.L., 2007. Prosocial development. In: Handbook of Child Psychology. John Wiley & Sons, Inc., p. 11

Fan, Y., Han, S., 2008. Temporal dynamic of neural mechanisms involved in empathy for pain: an event-related brain potential study. Neuropsychologia 46 (1), 160–173.

Fan, Y., Duncan, N.W., de Greck, M., Northoff, G., 2011. Is there a core neural network in empathy? An fMRI based quantitative meta-analysis. Neuroscience & Biobehavioral Reviews 35 (3), 903–911.

Fan, Y.-T., Chen, C., Chen, S.-C., Decety, J., Cheng, Y., 2013. Empathic arousal and social understanding in individuals with autism: evidence from fMRI and ERP measurements. Social Cognitive and Affective Neuroscience. http://dx.doi.org/10.1093/scan/nst101.

Ferreira-Garcia, R., Fontenelle, L.F., Moll, J., de Oliveira-Souza, R., 2013. Pathological generosity: an atypical impulse control disorder after a left subcortical stroke. Neurocase 20 (5), 496–500.

Gallese, V., Keysers, C., Rizzolatti, G., 2004. A unifying view of the basis of social cognition. Trends in Cognitive Sciences 8 (9), 396–403.

Helliwell, J.F., Putnam, R.D., 2004. The social context of well-being. Philosophical Transactions-Royal Society of London Series B Biological Sciences 1435–1446.

Hikosaka, O., Kim, H.F., Yasuda, M., Yamamoto, S., 2014. Basal ganglia circuits for reward value-guided behavior. Annual Review of Neuroscience 37, 289.

Hoult, T.F., 1984. Human sexuality in biological perspective: theoretical and methodological considerations. Journal of Homosexuality 9 (2–3), 137–155.

Hrdy, S.B., 2009. Mothers and Others: The Evolutionary Origins of Mutual Understanding. Harvard University Press.

Hwang, E.J., 2013. The basal ganglia, the ideal machinery for the cost-benefit analysis of action plans. Frontiers in Neural Circuits 7. http://dx.doi.org/10.3389/fncir.2013.00121.

Hyman, S.E., 2010. The diagnosis of mental disorders: the problem of reification. Annual Review of Clinical Psychology 6, 155–179.

Ickes, W., 1993. Empathic accuracy. Journal of Personality 61 (4), 587–610.

Ickes, W., 2001. Measuring empathic accuracy. Interpersonal Sensitivity: Theory and Measurement 219–241.

Kahneman, D., 2011. Thinking, Fast and Slow. Farrar Straus & Giroux, NY.

Kalev, A., Dobbin, F., Kelly, E., 2006. Best practices or best guesses? Assessing the efficacy of corporate affirmative action and diversity policies. American Sociological Review 71 (4), 589–617.

Kean, S., 2015. The man who couldn't stop giving. The Atlantic. Retrieved from: http://www.theatlantic.com/magazine/archive/2015/05/the-man-who-couldnt-stop-giving/389531/.

Lee, R.B., 1984. The Dobe! Kung. Holt Rinehart & Winston.

Lee, D., 2013. Decision making: from neuroscience to psychiatry. Neuron 78 (2), 233–248. http://dx.doi.org/10.1016/j.neuron.2013.04.008.

Leslie, A.M., Friedman, O., German, T.P., 2004. Core mechanisms in 'theory of mind'. Trends in Cognitive Sciences 8 (12), 528–533.

Lilienfeld, S.O., 2007. Psychological treatments that cause harm. Perspectives on Psychological Science 2 (1), 53–70.

Martin, D., March 1, 2004. Joan McCord, Who Evaluated Anticrime Efforts, Dies at 73. New York Times. Retrieved from: http://www.nytimes.com/2004/03/01/nyregion/01mccord.html.

Mathur, V., Harada, T., Lipke, T., Chiao, J., 2010. Neural basis of extraordinary empathy and altruistic motivation. NeuroImage 51, 1468–1475.

McCord, J., 1978. A thirty-year follow-up of treatment effects. American Psychologist 33 (3), 284.

McCord, J., 1979. Some child-rearing antecedents of criminal behavior in adult men. Journal of Personality and Social Psychology 37 (9), 1477.

McGrath, M., Oakley, B., 2012. Codependency and pathological altruism. In: Oakley, B., Knafo, A., Madhavan, G., Wilson, D.S. (Eds.), Pathological Altruism. Oxford University Press, New York, pp. 49–74.

Mendez, M.F., Chen, A.K., Shapira, J.S., Lu, P.-H., Miller, B.L., 2006. Acquired extroversion associated with bitemporal variant of frontotemporal dementia. Journal of Neuropsychiatry and Clinical Neurosciences 18 (1), 100–107.

Moll, J., de Oliveira-Souza, R., Moll, F.T., Ignácio, F.A., Bramati, I.E., Caparelli-Dáquer, E.M., Eslinger, P.J., 2005. The moral affiliations of disgust: a functional MRI study. Cognitive and Behavioral Neurology 18 (1), 68–78.

Moll, J., Krueger, F., Zahn, R., Pardini, M., de Oliveira-Souza, R., Grafman, J., 2006. Human fronto–mesolimbic networks guide decisions about charitable donation. Proceedings of the National Academy of Sciences 103 (42), 15623–15628.

Nágera, A.V., 1944. Tratado de psiquiatría. Salvat Editores S. A.

Neuberg, S.L., Cialdini, R.B., Brown, S.L., Luce, C., Sagarin, B.J., Lewis, B.P., 1997. Does Empathy Lead to Anything More Than Superficial Helping? Comment on Batson et al.

Neusner, J., Chilton, B., 2005. Altruism in World Religions. Georgetown University Press, Washington, DC.

Nowak, M.A., Tarnita, C.E., Wilson, E.O., 2010. The evolution of eusociality. Nature 466 (7310), 1057–1062.

Oakley, B., Knafo, A., Madhavan, G., Wilson, D.S. (Eds.), 2012. Pathological Altruism. Oxford University Press, New York, NY.

Oakley, B.A., 2013. Concepts and implications of altruism bias and pathological altruism. Proceedings of the National Academy of Sciences 110 (Suppl. 2), 10408–10415.

Oakley, B., 2014. Empathy in academe: on the origins of pathological altruism. Academic Questions 27 (1), 48–64. http://dx.doi.org/10.1007/s12129-013-9403-2.

O'Sullivan, S.S., Evans, A.H., Quinn, N.P., Lawrence, A.D., Lees, A.J., 2010. Reckless generosity in Parkinson's disease. Movement Disorders 25 (2), 221–223.

Petrosino, A., Turpin-Petrosino, C., Finckenauer, J.O., 2000. Well-meaning programs can have harmful effects! Lessons from experiments of programs such as scared straight. Crime & Delinquency 46 (3), 354–379.

Petrosino, A., Turpin-Petrosino, C., Buehler, J., 2003. Scared Straight and other juvenile awareness programs for preventing juvenile delinquency. The Annals of the American Academy of Political and Social Science 589 (1), 41–62.

Premack, D., Woodruff, G., 1978. Does the chimpanzee have a theory of mind? Behavioral and Brain Sciences 1 (04), 515–526.

Prinz, J., 2011. Is empathy necessary for morality? In: Goldie, P., Coplan, A. (Eds.), Empathy: Philosophical and Psychological Perspectives. Oxford University Press, New York, NY, pp. 211–229.

Psychwikicom. Prosocial behavior. Retrieved from: http://www.psychwiki.com/wiki/Prosocial_Behavior.

Rameson, L.T., Morelli, S.A., Lieberman, M.D., 2012. The neural correlates of empathy: experience, automaticity, and prosocial behavior. Journal of Cognitive Neuroscience 24 (1), 235–245.

Riby, D., Bruce, V., Jawaid, A., 2012. Everyone's friend? The case of Williams syndrome. In: Oakley, B., Knafo, A., Madhavan, G., Wilson, D.S. (Eds.), Pathological Altruism. Oxford University Press, New York.

Rifkin, J., 2009. The Empathic Civilization: The Race to Global Consciousness in a World in Crisis. Penguin, NY.

Sander, R., Taylor Jr., S., 2012. Mismatch. Basic Books, NY.

Sanstock, J.W., 2007. A Topical Approach to Life-Span Development. McGraw-Hill, New York.

Schroeder, D.A., Graziano, W.G., 2015. The Oxford Handbook of Prosocial Behavior. Oxford University Press.

Shamay-Tsoory, S.G., 2010. The neural bases for empathy. The Neuroscientist 17 (1), 18–24. http://dx.doi.org/10.1177/1073858410379268.

Siegal, M., Varley, R., June 2002. Neural systems involved in 'Theory of Mind'. Nature Reviews Neuroscience 3 (6), 463–471.

Straubhaar, J., LaRose, R., Davenport, L., 2013. Media Now: Understanding Media, Culture, and Technology. Cengage Learning.

Sunstein, C.R., Vermeule, A., 2005. Is Capital Punishment Morally Required? The Relevance of Life-Life Tradeoffs. U Chicago Law & Econ, pp. 05–06. Olin Working Paper (239).

Titchener, E.B., 1909/2014. Introspection and empathy. Dialogues in Philosophy, Mental and Neuro Sciences 7 (1), 25–30.

Vischer, R., Fiedler, C., Wolfflin, H., Goller, A., Hidebrand, A., Schmarsow, A., 1993. Empathy, Form, and Space: Problems in German Aesthetics, 1873–1893 (H.F. Mallgrave & E. Ikonomou, Trans.). Getty Center for the History of Art and the Humanities.

Walter, H., 2012. Social cognitive neuroscience of empathy: concepts, circuits, and genes. Emotion Review 4 (1), 9–17.

Wilson, T., 2011. Redirect: The Surprising New Science of Psychological Change. Little, Brown and Company, New York, NY.

Wilson, D.S., 2015. Does Altruism Exist? Culture, Genes, and the Welfare of Others. Yale University Press, New Haven, CT.

Wright, R., Cummings, N. (Eds.), 2005. Destructive Trends in Mental Health. Brunner-Routledge, New York, NY.

Wright, R., 1994. The Moral Animal: The New Science of Evolutionary Psychology. Pantheon Books, New York.

Wu, N., Su, Y., 2015. Oxytocin receptor gene relates to theory of mind and prosocial behavior in children. Journal of Cognition and Development 16 (2), 302–313.

Zaki, J., Ochsner, K., 2012. The neuroscience of empathy. Nature Neuroscience 15 (5), 675–680. http://dx.doi.org/10.1038/nn.3085.

Zaki, J., Bolger, N., Ochsner, K., 2008. It takes two the interpersonal nature of empathic accuracy. Psychological Science 19 (4), 399–404.

Zaki, J., Bolger, N., Ochsner, K., 2009a. Unpacking the informational bases of empathic accuracy. Emotion 9 (4), 478.

Zaki, J., Weber, J., Bolger, N., Ochsner, K., 2009b. The neural bases of empathic accuracy. Proceedings of the National Academy of Sciences 106 (27), 11382–11387.

Chapter 22

Cognitive Ethology and Social Attention

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INTRODUCTION

The seed for this chapter was originally sown in the 1980s when the lead author (Alan Kingstone) was an undergraduate student volunteering in an animal learning laboratory that used black hooded rats to investigate the processes and mechanisms of human cognition. The two fundamental assumptions of that work were that (1) humans and other animals have much in common and (2) by controlling and manipulating the environment of the latter, and measuring the resultant behavior, one could discover principles of cognition that scale up and apply to humans. When Alan Kingstone went to graduate school, he cut out the nonhuman middleman and studied human cognition directly. But the field's basic research assumptions were the same: (1) human cognition is subserved by processes that are stable across different environments (just as they were assumed to be invariant across different species), and (2) one can maximize analytical power in the investigation of cognitive processes by minimizing all variability in a situation save for the factor that is being manipulated.

These working assumptions were best exemplified by Michael Posner's book *Chronometric Explorations of Mind* (1978), which had established itself as a classic text in the 1980s for those studying human cognition and attention. According to Posner, the key for revealing the fundamental mechanisms of the mind and brain was to develop a simple model task that could be applied broadly with any number of different populations (eg, infants, aged, patients) and measures (eg, behavior and brain imaging). For Posner, the model task was the attention-cuing paradigm (Posner, 1980), which researchers now call the "Posner paradigm." As this paradigm has been used perhaps more than any other task in attention research (eg, visual search, inhibition of return, change blindness, etc.), and because it plays a foundational role in the field of social attention research, we will consider it in some detail.

In the Posner paradigm, a central fixation point is flanked by two boxes in the center of a computer screen. The participant's task is simply to press the space bar on a computer keyboard as quickly as possible when a visual target object appears inside either one of the boxes. This target object is preceded by what is called an attentional cue, which is either a brief peripheral flash surrounding one of the two boxes (Fig. 22.1A), or a central arrow pointing toward one of the boxes (Fig. 22.1B).

Because the brain processes attended items more quickly than unattended items, target detection time can be used to determine where attention is allocated. In the Posner paradigm, the standard finding is that target detection time is faster when a target appears at the cued location (ie, the box that brightens or is pointed at by the arrow) than the uncued location (ie, the box that does not brighten or is not pointed at by the arrow). These results indicate attention being allocated to the cued location and away from the uncued location.

Despite the common pattern of results generated by central directional and peripheral cues, the kinds of attentional orienting the cues engage are thought to be very different. When one of the two boxes is flashed briefly, as depicted in Fig. 22.1A, people are faster to detect a target in the flashed box, even when the flash does not predict where the target will occur (ie, the target appears in the cued box 50% of the time and in the uncued box 50% of the time). Because participants have no good reason to expect the target to appear at the cued/flashed location versus the uncued/unflashed location, but they nevertheless shift their attention to the cued location, researchers have taken this result as evidence that the flash "pulls" attention to the cued location in a manner that is beyond the control of the participant. This type of reflexive orienting is often called

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00022-3

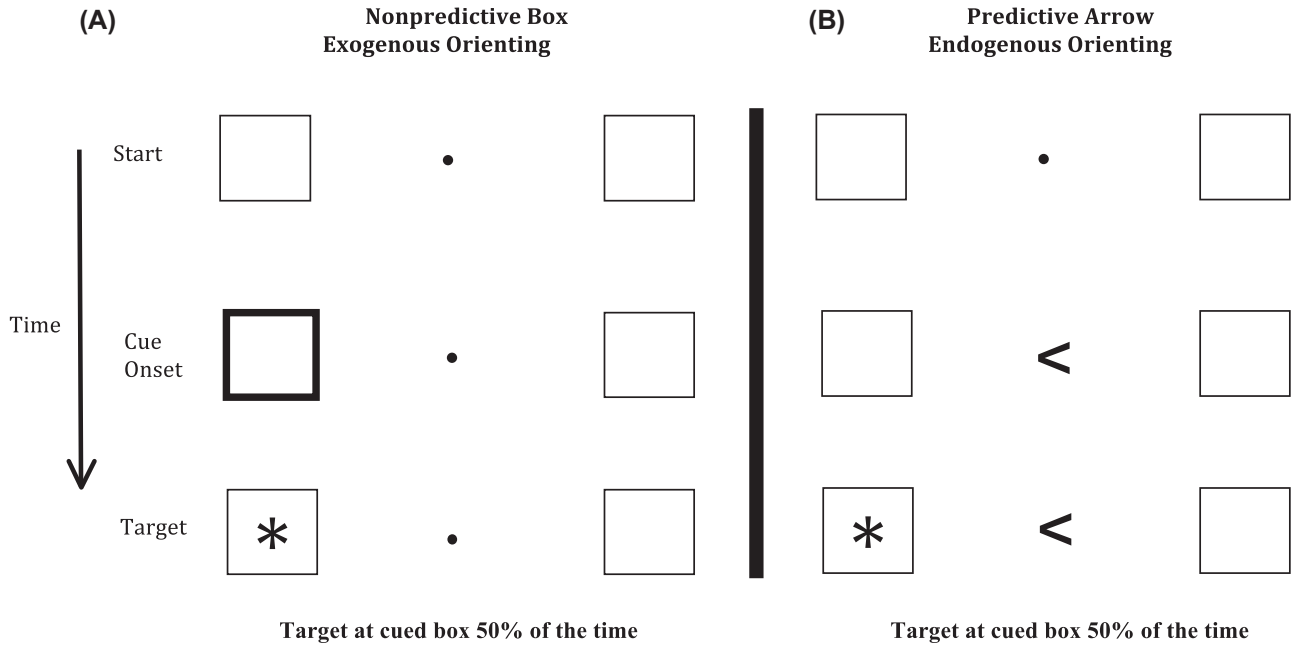

FIGURE 22.1 Examples of a Posner cueing task. Each panel presents three stages of a typical trial: start, cue onset, and target onset. In these examples, the target (a *small black asterisk*) demanding a speeded response, appears at either the cued location or the uncued location. (A) The peripheral cue does not reliably predict where the target will appear; (B) the *central arrow* cue is spatially predictive.

exogenous, bottom-up, or stimulus-driven attentional orienting because the orienting is initiated by an environmental event rather than by the participant.

In contrast, when a central arrow points toward one of the two boxes, as depicted in Fig. 22.1B, attention is thought to be oriented volitionally to the box pointed at by the arrow. This attention shift is considered an endogenous or top-down form of orienting in that the participant has some control over the initial orienting behavior. In support of this view, initial reports (Jonides, 1981) indicated that when cued by a central arrow, target detection is faster at the cued location but only when the arrow points to the location where the target will occur at a rate that is far above chance (eg, 80% of the time the target appears at the cued location and 20% of the time in the uncued location). In other words, because the cue is spatially predictive (eg, valid 80% of the time) a participant is willing to "push" attention volitionally to the cued location which in turn leads to faster target detection at the cued versus uncued location.

Since the 1980s, countless studies have used this model task, or some variation of it, to discern the basic mechanisms of exogenous and endogenous attention. These investigations include, but are in no way limited to, studies with infants and children, healthy adults and aged individuals, brain-lesioned patients, as well as single cell and neuroimaging investigations (see Carrasco, 2011, for a recent review).

Despite the wide application of the Posner paradigm, one might reasonably ask: what does detecting a light at a cued or uncued location have to do with the many rich experiences that people share every day, such as chatting with a friend or driving a car to work? On the face of it, the answer is not very much. Nevertheless, as noted above, the assumption is that the principles of human attention and behavior studied in the laboratory using model tasks like the Posner paradigm will shed light on those cognitive processes as they operate in everyday situations. In the words of one of the top researchers in the field: "A man does not use one brain in the laboratory and another in the rest of his life" (Broadbent, 1971, p. 3). While the statement is obviously true, it does not necessitate that there is a direct relationship between the principles inferred from performance on a simple laboratory task and the principles governing performance during complex everyday situations.

The concern that laboratory tasks may not capture important aspects of everyday behavior was addressed by Kingstone et al. (2003) when they noted that, among other things, the world that people live in is an inherently social one, and that testing people in isolation with simple arbitrary symbolic stimuli may be, at best, missing a significant part of the bigger picture, or at worst getting things altogether wrong. To illustrate this point, they reported that strange and unexpected things happen when one introduces two small modifications to the Posner paradigm. Generally

speaking, these changes serve to switch the Posner paradigm from an asocial task to one that includes some social context (eg, Friesen and Kingstone, 1998; Driver et al., 1999; Langton and Bruce, 1999). Their first change was to replace the left and right arrows with a schematic face with eyes directed to the left or right. The other change was to eliminate the predictive value of the central cue for the location of the target, so that participants would have no reason to attend volitionally to where the eyes were directed (Fig. 22.2). Note that because the eyes were centrally located and spatially nonpredictive, the prediction—derived from thousands of studies using the Posner paradigm—was that participants would not volitionally shift attention to the cued/gazed-at location (ie, central directional cues, like arrows, need to be spatially predictive to produce orienting; Jonides, 1981).

However, the results were altogether different from what was expected. Participants shifted their attention to where the eyes were directed, despite the fact that they knew that the eyes did not predict where a target would occur. Even after receiving hundreds of trials with this irrelevant social cue, participants would continue to shift attention to the location gazed at by the eyes of the schematic face (ie, targets were detected faster when they appeared at the location that the eyes looked at rather than the one to which the eyes were not directed). In short, the behavioral predictions borne out of research using the Posner paradigm failed to correctly predict how people would perform when a simple social modification was introduced. This result seemingly casts doubt on the prospect that the principles derived from this simple, Spartan paradigm would scale easily to how attention operates in our complex, social environments.

As an aside, these new social cuing data encouraged researchers to revisit the original work with the Posner paradigm, which revealed that contrary to the original assumption that nonpredictive arrow cues fail to produce exogenous orienting, it is now generally accepted that they do, albeit it is generated differently from what is observed using gaze cues (Friesen et al., 2004; Ristic et al., 2007). Note the implication of the finding that nonpredictive arrows produce orienting is that several decades of attention research and thousands of studies using the Posner paradigm have been misinterpreting their own results: though they thought that they were measuring volitional attention and the brain mechanisms that subserve it, they were in fact measuring something altogether very different (cf. Ristic and Kingstone, 2006, 2009, 2012; Olk et al., 2008, 2010; Olk and Kingstone, 2015).

To summarize, attention research has traditionally sought to simplify the issue of investigation by making the experimental context both impoverished and controlled. The hope is that by minimizing the complexity of the environment and maximizing experimental control, investigators can generate theories that will apply successfully across different contexts. The Posner cueing paradigm is a classic representation of this approach. Yet, as suggested above, the greater promise (ie, general theories of how attention functions beyond the laboratory) does not seem to be on the horizon. It is important to note that while the focus here has been on the Posner paradigm, the same underlying assumptions form the bedrock of other model paradigms in cognitive science (eg, visual search, inhibition of return, oculomotor capture, and the attentional blink to name some of the more popular model tasks in the field) and as a result they all suffer the same shortcomings.

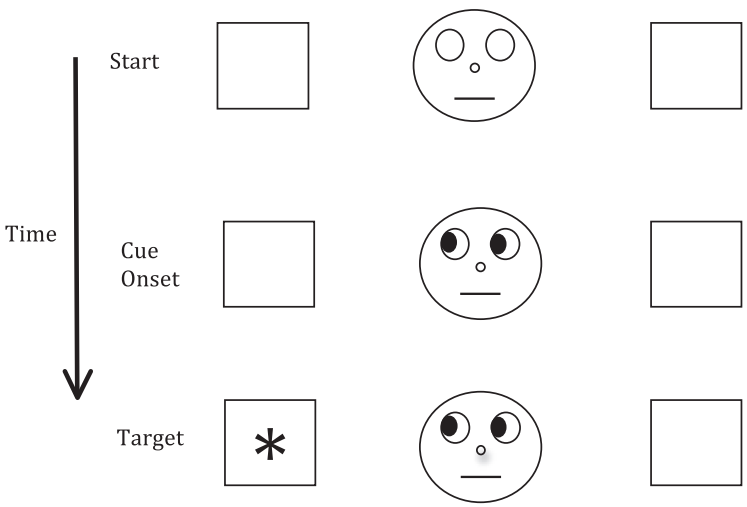

FIGURE 22.2 Example of a gaze cueing task. Each panel presents three stages of a typical trial: start, cue onset, and target onset. In these examples, the target (a *small black asterisk*), demanding a speeded response, appears at either the cued location or the uncued location. Note that the direction of the eye gaze does not reliably predict where the target will appear.

That is, they all assume that cognitive processes are relatively stable across situations and as such can be best understood by simplifying the environment in order to impose rigorous experimental control. These assumptions have justified—and even necessitated—studying human cognition and behavior in extremely controlled, simplified, and artificially contrived laboratory paradigms. But if cognitive processes turn out not to be quite as invariant as assumed and/or some of the features of everyday cognition that are "simplified away" turn out to be fundamental, then this kind of approach is likely to yield "fragile" principles that fail to predict behavior across a range of contexts. The example above, involving the theoretical difficulties caused by the simple introduction of an everyday social stimulus into the traditional Posner paradigm, suggests that, in fact, the basic approach might not be yielding the general principles we had hoped.

Given the difficulties outlined above, it might be time to take seriously the idea that cognitive processes vary and are affected by what is happening elsewhere within the cognitive system. As such, the operation of a given cognitive process will depend critically on the specific situational context in which a subject is embedded. Studying individuals in isolation on simple tasks are destined to generate principles of cognition that, while internally valid, lack the ability to survive across different situations, especially those that occur during the natural complexities of everyday life.

If there are both practical and principled reasons to conclude that lab-based studies grounded on the assumptions of invariance and simplification are unlikely to shed light on cognitive processes as they are expressed in real-life situations, then what are researchers to do? Historically the field's response has generally taken one of the two forms. One reaction is to deny that there is a problem. This response enables one to maintain the initial assumption that cognitive processes are invariant and that our Spartan tasks are capturing their basic function, and thus allows one to continue to create and study laboratory-specific phenomenon under the guise that the results are relevant at a broader level. The other reaction is to acknowledge that there is a problem, but then continue to conduct research predicated on the same assumptions. Both responses are what Broadbent (1991) has called "pathological."

Occasionally, investigators, such as Donald Broadbent and Ulric Neisser have tried a third response. They acknowledged that cognitive processes are influenced by situational changes that in many cases are not captured by the simplified and well-controlled tasks and worked hard to bring the implications of this fact to the awareness of others. But without an alternative research approach, investigators in the 1990s struggled to avoid slipping into one of the two pathological responses of the past. However, alternative approaches are now beginning to emerge, one of which is called cognitive ethology. We describe this approach, and some of its findings, in the next section.

COGNITIVE ETHOLOGY

The fact that cognitive processes can change with the situational context in which a subject is embedded presents a serious challenge to researchers hoping to generalize their work to our everyday cognitive lives. In response, many have chosen to redefine the scope of their research objectives to understanding how a particular phenomenon, such as inhibition of return, behaves only in a laboratory setting (Klein, 2000), whereas some have emphasized the importance of investigating behavior that emerges within more natural contexts, typically involving a complex analysis of coordinated sequences of actions (Ballard and Hayhoe, 2009; Ballard et al., 1995; Hayhoe and Ballard, 2005; Land and Lee, 1994; Land and Hayhoe, 2001; Land and McLeod, 2000).

In addition to these approaches, others have begun to embrace the fact that cognition varies with situational context and have turned it into the very focus of their laboratory enterprise, as is the case with some within the embodied, situated, and distributed cognition traditions (eg Glenberg, 2010; Hollan et al., 2000; Hutchins, 1995; Killeen and Glenberg, 2010; Aydede and Robbins, 2009; Wilson, 2002). Cognitive ethology represents such a response (Kingstone et al., 2003; Kingstone et al., 2008; Kingstone, 2009; Smilek et al., 2006). Although the cognitive ethology approach shares elements with others that emphasize the need to understand behavior in more natural contexts (Ballard et al., 1995; Land and Hayhoe, 2001), its aim is to provide research scientists with a methodology for bridging the gap that exists between uncontrolled real-life phenomena and controlled laboratory investigation, so that the effect studied in the lab can make direct and relevant contact with everyday life. In a nutshell, cognitive ethology proposes that one should ideally study a phenomenon both as it naturally occurs within a complex real-world environment as well as in more simplified and controlled lab-based situations. By combining investigations at a more naturalistic level with those in a more controlled research environment, one can determine which lab-based findings are likely to scale up to a natural environment and which findings are specific to a controlled research environment.

While the general reader might find the proposal of cognitive ethology to be self-evident and simply involve the application of basic scientific common sense, it is instructive to remember that historically, laboratory research in the field of human cognition has been founded on the critical assumptions that human cognition is subserved by processes that are invariant across situations.

Taking this as a given together with the notion that experimental control improves internal validity, it follows that those processes are therefore best understood in simplified and controlled experimental situations. The former invariance assumption enables one to conduct a study in the laboratory and then to propose that the process being measured will be expressed in everyday life. The second assumption is derived from the first: given that processes are assumed to be invariant across situations, it follows that one can reduce situational variability, thereby maximizing analytical power, without compromising the nature of the process one is measuring. Together these assumptions drive a researcher away from the complexities of everyday life while at the same time enabling one to make the claim that the process in question operates identically in everyday life as in the lab, without any need or even obligation to test or confirm that the claim is valid.

In contrast, cognitive ethology rejects the standard assumption of invariance and the sufficiency of using the simplified, highly controlled tasks that it engenders for making claims about human cognition that are likely to scale up to more naturalistic contexts. In their place, this approach embraces the notion that cognition and behavior are highly context dependent and that much can be learned by observing, describing, and measuring what people do and experience in an uncontrolled natural situation of interest. In other words, the approach is characterized by loosening the assumptions of invariance and the need for control for the scientific and objective study of human behavior under natural conditions. The goal is not to eliminate lab-based studies but to build a clear connection between what occurs naturally in everyday life and the experiments that are conducted under more controlled conditions.

One way to employ a cognitive ethology methodology is to start with a simple lab study and then steadily increase the situational complexity to determine if, or when, the results and conclusions start to change. In our own lab we have employed such an approach with regard to social attention. Below, we summarize some of the key findings of this work as it progresses systematically upwards in a range of complexity toward a comparison against real-life behavior.

COGNITIVE ETHOLOGY: LAB TO LIFE

Images of One Person

When looking at another's face, fixations tend to cluster around the internal features, which include the eyes, mouth, and nose (Henderson et al., 2005; Walker-Smith et al., 1977). Of these, the eyes are the most frequently fixated (Henderson et al., 2005; Pelphrey et al., 2002; Walker-Smith et al., 1977; Yarbus, 1967). That people show a bias to attend to another's eyes is not altogether surprising. After all, the eyes provide the looker with valuable social information about a person's intentions, emotions, and attentional focus. Indeed, in our lab we have been hard pressed to find a task that gets people to stop looking at the faces and eyes of the individuals in the scenes. For instance, Laidlaw et al. (2012) presented participants with a series of upright and inverted faces. Participants were simply asked to look at the faces as they normally would (free-viewing) or instructed to avoid looking at either the eyes, or as a control, the mouth. For both upright and inverted faces, participants showed a strong bias to attend to the eyes and the mouth during free-viewing (though the bias was far stronger for the eyes; see Fig. 22.3). When the participants were instructed

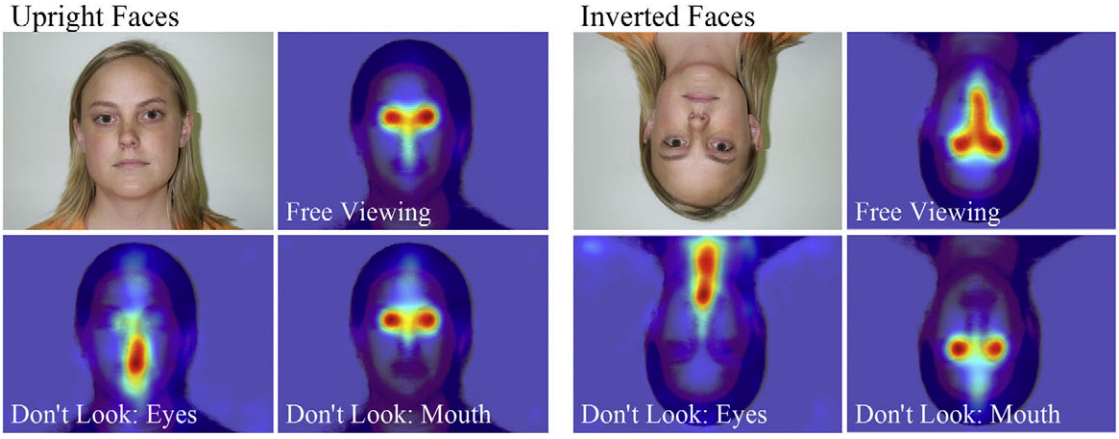

FIGURE 22.3 Heat maps representing average locations of participants' fixations for upright and inverted faces in Free Viewing, Don't Look: Eyes, and Don't Look: Mouth conditions. *Warmer colors* denote greater overlap across participant fixations. *Adapted with permission from Laidlaw, K.E.W., Risko, E.F., Kingstone, A., 2012. A new look at social attention: orienting to the eyes is not entirely under volitional control. Journal of Experimental Psychology: Human Perception & Performance 38, 1132–1143.*

to avoid looking at the mouth, they were able to do this without fail, typically by directing their gaze to the eyes of the faces. However, when instructed to avoid looking at the eyes, participants were able to eliminate looks to the eyes for the inverted faces but were not completely successful when the faces were upright. Taken together, these results suggest that there is a reflexive tendency to look at the eyes when a face is upright. Moreover, as holistic processing is strongest with upright faces and weaker or even absent with inverted faces (Yovel and Kanwisher, 2005), it appears that nonvolitionally orienting to the eyes requires holistic face processing.

That there is a bias to look at the eyes when a face is presented in isolation begs the question of whether the bias is still measurable when selection of the feature is made more complex. When looking at faces in isolation, holistic face processing may drive fixations to the middle of peoples' faces. It follows then that people may attend to the eyes of others based on convenience: they are the closest feature to where the eyes naturally land (Andrews et al., 2010; Bindemann et al., 2009). Alternatively, eye selection may be so critical to our social lives that others have argued for a distinct neural module (for example, within the superior temporal sulcus, or STS) that is uniquely tuned to the eyes of others, regardless of how they are presented on the face, or elsewhere on a stimulus (eg, Akiyama et al., 2006).

A study by Levy et al. (2012) aimed to distinguish between these two accounts. Observers were presented with images of people, nonhuman creatures with eyes in the middle of their faces ("humanoids"), or creatures with eyes positioned in abnormal locations, such as on their hands ("monsters"). There was a profound and significant bias toward looking early and often at the eyes of humanoids. Critically, this bias was also present for looking at the eyes of monsters demonstrating that the selection bias for the eyes is not for the middle of a person's face but for their eyes. These data strongly support the idea that the human brain is specialized for acquiring social, behaviorally relevant information from others: we can quickly, and even nonvolitionally (Laidlaw et al., 2012), select for the gaze of others, even when the location of the eyes is atypical. As gaze selection is the key precursor to gaze following, which is common to both humans and nonhuman primates, it is reasonable to speculate that this behavior is subserved by a neural system that is shared across primates (Emery, 2000; Deaner and Platt, 2003), with both lesion and functional neuroimaging studies implicating the STS as a likely seat of this ability (see Birmingham and Kingstone, 2009 for a recent review; Calder et al., 2007; Campbell et al., 1990; Heywood et al., 1992; Hoffman and Haxby, 2000; Kingstone et al., 2004).

Images of People

To date the studies we have considered have investigated how people look at images depicting isolated faces or bodies of people (and monsters). Indeed, in the literature there are very few studies that have examined how people look at photos that contain people as well as a host of other things to be fixated (eg, chairs, tables, doors, lamps, and so forth). Indeed, in many scene perception studies, which seem ideally suited to test for a bias toward social stimuli, researchers often exclude social scenes (ie, those containing people) for fear of those social stimuli unduly influencing observers' attentional allocation. But this idea—that people would preferentially attend to other people at the expense of other visually complex stimuli—had until recently remained relatively untested (though see Yarbus, 1967). More than this, might people preferentially attend to certain features of people in complex scenes? Stated differently, if eyes have a privileged status when they are presented as part of an isolated face or person, is it also the case that they will be preferentially selected when scene complexity is increased? To test this within the philosophy of a cognitive ethology approach of increasing situational complexity, while also reducing experimental control, we gave people a host of different social scenes to look at and avoided giving participants any specific task (Birmingham et al., 2008a,b). Specifically, participants were presented with real-world photographs of people engaged in a variety of natural social situations (eg, a person sitting alone or with others drinking coffee, people looking at and sharing a menu, and so forth). Their instruction was to simply "look at these photos the way you normally would."

Despite the increase in stimulus complexity and decline in instructional control, the results of this work showed that observers looked mostly at the eyes, and looked relatively infrequently at the rest of the scene (eg, bodies, foreground objects, background objects). These investigations also found that attention to the eyes of others could be modulated by social factors. For instance, observers selected the eyes more frequently in scenes high on social content, that is, scenes containing multiple people doing something together, as compared to scenes with multiple people not interacting or scenes with only one individual performing an activity. In addition, attention to the eyes of others increased when observers were indirectly prompted to focus on social aspects of the scene (eg, when asked to report what the people in the scenes are thinking) relative to when performing other less socially focused tasks, such as describing the scenes in general (Birmingham et al., 2008b; see also Smilek et al., 2006).

Finally, and perhaps most importantly, Birmingham et al. (2009) demonstrated that when these complex social scenes are presented to observers, they quickly fixate the eyes of the people in the scenes independent of their

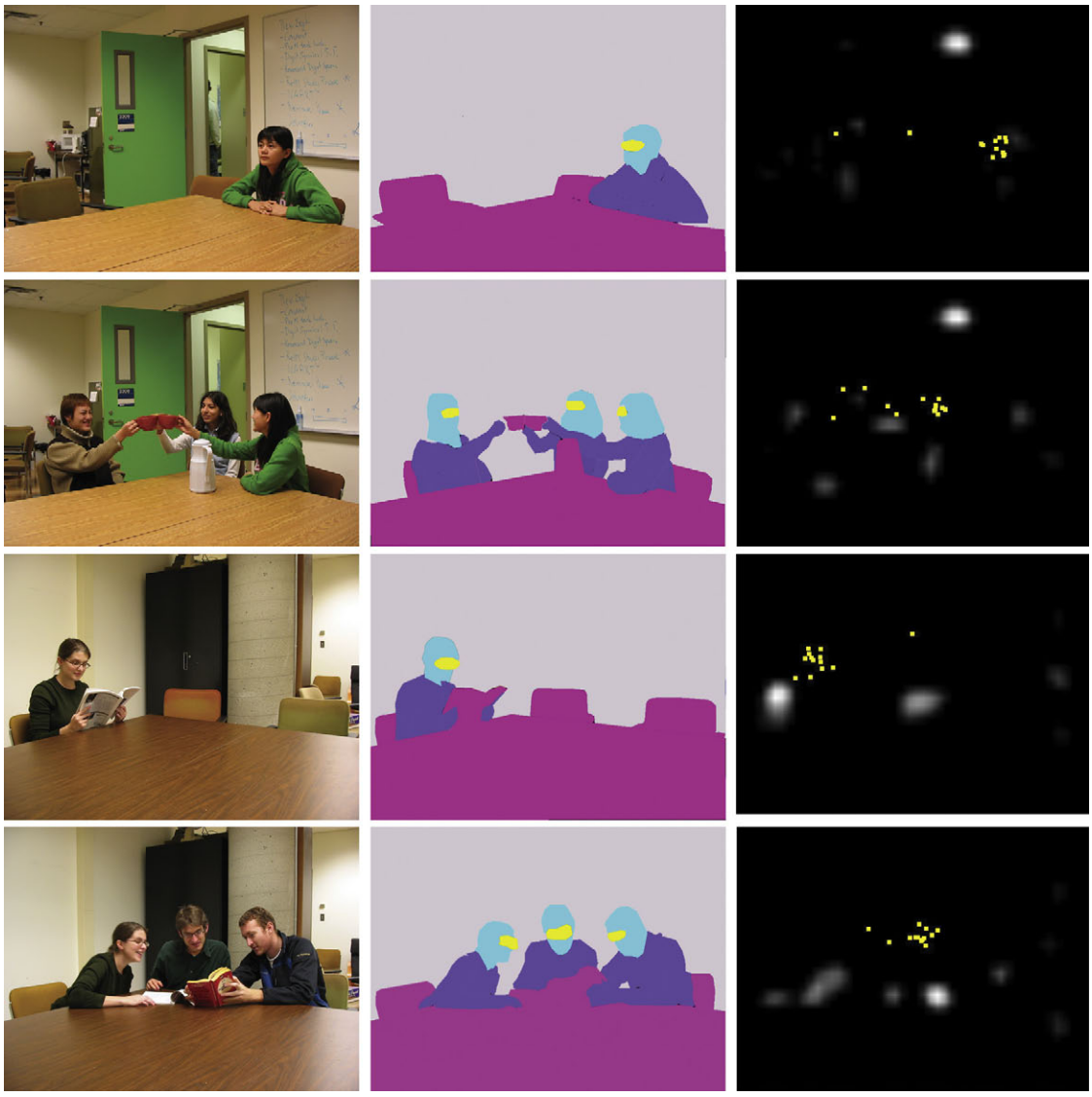

FIGURE 22.4 The general regions defined (eyes, heads, bodies, foreground objects, and background) and their corresponding saliency maps (*white areas* indicate regions of higher saliency) overlaid with the first fixations (*yellow points*). *Adapted with permission from Birmingham, E., Bischof, W.F., Kingstone, A., 2009. Saliency does not account for fixations to eyes within social scenes. Vision Research 49, 2992–3000.*

objective stimulus saliency (see Fig. 22.4). This is noteworthy because until very recently it was held that where people look could largely be explained by the visual primitives that are salient in a scene (Itti and Koch, 2000). The saliency model from Itti and Koch (2000), which was derived from scenes that rarely contained people, assumes that where people look in photos is determined by a "winner take all" visual saliency map (eg, luminance, contrast, color in the scenes) above and beyond any other features of the image. This model suggests that once the most salient region is fixated, it is inhibited for a period of time and the next eye movement is made to the next most salient region, and so forth. The work of Birmingham et al. (2009) invalidates this saliency model (see also Foulsham and Underwood, 2007, 2008). Thus by increasing stimulus complexity and reducing experimental control, a prevailing model of human attention is found wanting.

As an interesting aside, this disconfirmation of the saliency model echoes a similar fate to that of the Posner paradigm. In both cases, substantive methods and models in the field of cognition and attention are found incapable of accurately predicting performance when a social element is introduced into the experimental situation. That said, to date, the research presented here has been a rather narrow representation of a cognitive ethology approach. To be sure, we have progressed in terms of stimulus complexity from photos of faces in isolation to photos of people with other people, and in terms of experimental

control we have loosened the grip from telling people where not to look to instructing them to view stimuli as they please, but still, the upshot is that the participants are simply looking at static images on a computer screen. Therefore the next step was to examine if the bias to look at the eyes of others persists when participants are presented with dynamic images (ie, video), and if it does, to take a step into the real world.

Dynamic Images of People

In real life people move about, they look at each other, and they talk to one another. As noted above, to date the research showing a bias to look at the eyes of people has been based entirely on static images. What happens when observers are shown scenes of people moving and talking? Foulsham et al. (2010) (see also Cheng et al., 2013) asked precisely this question. Participants watched videos of different groups of three individuals sitting around a table discussing a hypothetical situation regarding the most important items that they would take to the moon (see Fig. 22.5). What Foulsham et al. (2010) found is that despite the fact that these groups were highly dynamic, there was a tremendous consistency in the observers' looking behavior both in terms of location and timing, with participants primarily looking at the eyes of the people in the video. Interestingly, this result held even when the social status of the people in the scenes was taken into account. That is, although the people judged to be of higher status were looked at more than those of lower status, it was the person's eyes that observer's tended to fixate on most, regardless of their status.

It is also noteworthy that, as was the case with the Birmingham et al. (2009) studies, these findings cannot be explained in terms of basic low-level stimulus saliency, provided these video stimuli included features like visual motion and sound onsets. Foulsham and Sanderson (2013) and Coutrot and Guyader (2014) both investigated whether looks to the faces and eyes of individuals engaged in conversation are significantly affected by changes in visual saliency, or whether the audio is present or absent. Their results indicated that the addition of an audio track increased looks to the faces and eyes of the talkers, and also resulted in greater synchrony for when the observers looked at the speakers (Foulsham and Sanderson, 2013). Critically, however, whether sound was present or not, and independent of changes in low-level visual saliency (Coutrot and Guyader, 2014), people spent most of their time looking at the faces and eyes of the individuals in the videos.

Collectively, these data converge on the conclusion that there is a preferential bias to attend to the eyes of others, and this bias generalizes across all levels of complexity, from static images of single faces to photos containing multiple people immersed among other objects, to dynamic scenes of groups of people talking and interacting. This kind of generalization of what clearly is a rich and robust

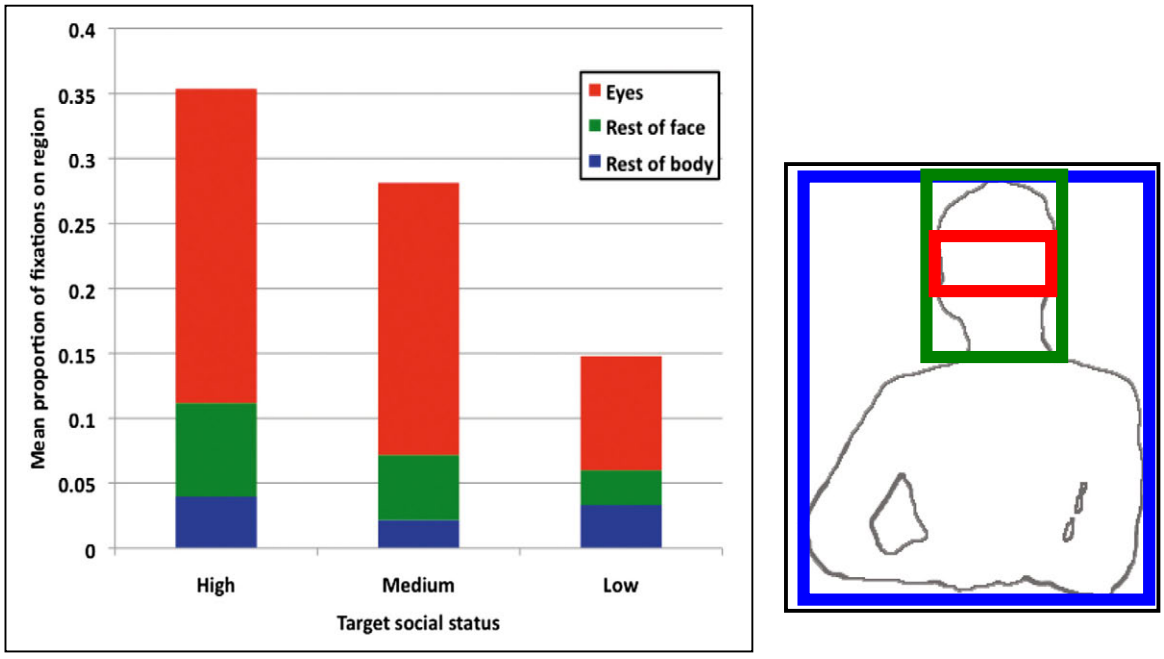

FIGURE 22.5 The amount of gaze given to different parts of the people was accomplished by defining moving areas of interest for the eyes and head (the relative sizes of which are depicted with a diagram of one target in the right panel). The proportion of fixations on each of these regions, averaged across all observers, is shown in the left panel. *Adapted with permission from Foulsham, T., Cheng, J.T., Tracy, J.L., Henrich, J., Kingstone, A., 2010. Gaze allocation in a dynamic situation: effects of social status and speaking. Cognition 117, 319–331.*

effect is quite impressive. And naturally the strong implication is that what we are finding in the lab across all these different levels of complexity and control will also be found to occur in real life. The methodology of the cognitive ethology approach, however, demands that findings in the lab be tested against real life performance, as it is possible that there are one or more factors in real life that are not being captured in the lab. As we shall see, this is precisely the case.

COGNITIVE ETHOLOGY: LIFE TO LAB

According to cognitive ethology, when measuring performance at the real-world level, one wants to minimize experimental control, thereby freeing the individual to do what they would naturally do. Our initial foray into research at this level of investigation went as follows. Upon entering the lab participants were given five dollars and asked to walk across the university campus to a cafe and buy themselves a treat (eg, a pastry or coffee), and then to return to the lab. The entire journey took about 30 min. Participants wore an eye tracker that recorded a field view of their trip (video and audio) as well as what they looked at during the journey. Several days later, participants returned to the lab and this time they watched videos of their own walk and the recording from the trip of others, while having their eye movements monitored. This allowed us to compare where participants looked when they were actually walking across the campus versus where they looked when they were watching a video of the trip.

Based on what we have seen so far, the strong prediction is that participants will look at the eyes of the people on the campus both when they are actually making the walk across campus, and purchasing their treat, and when they are watching a video recording of the trip. However, this is not what Foulsham et al. (2011) found. What we discovered is that when people were watching the video of their own trip, or the trip taken by someone else, they tended to look at the people—especially their eyes. This is, of course, exactly what we would expect to find based on previous research. However, this is not exactly what we found for people who were actually walking across campus. To be sure, there was a marked tendency to look at people in real life but this was limited to when they were far away from the participant. As people came nearer, the participants would look away. Note this is not what happened when the same individuals were in the lab and watching videos of their own trip and that of other participants. When watching a video, the participants were all too willing to look at another person as they approached, and then to continue to look at them while they walked past.

What is going on? Our intuition, and possibly the reader's as well, is that the difference between these two conditions is not just a difference in stimulus complexity. Rather, a key difference between watching a person walk past you in a video, and having a person walk past you in real life, is that in real life there is the potential to interact with the person, whereas this is not possible for the person on the video.

To test this hypothesis, we again applied the cognitive ethology approach and tried to recreate in the lab the phenomenon that we had just observed in real life. To do this we measured participants' looking behavior as they were sitting in a waiting room, either in the presence of a confederate posing as another research participant, or in the presence of a videotape of the same confederate (see Fig. 22.6). Thus, the potential for social interaction existed only when the confederate was physically present. While wearing a mobile eye tracker, participants waited in a room for about 2 min, under the guise that the experimenter had stepped out to collect materials necessary for the study to begin. In this way, participants were unaware that the 2-min waiting period was part of the experiment. In the room, there was either a confederate sitting to their left, quietly completing a questionnaire, or a video of the same confederate from a different session playing on a computer screen to the participants' right-hand side. The computer station was set up to look as though a research assistant had left the video playing and stepped out of the room. Participants' eye movements were coded for looks to the confederate (either videotaped or live; coded for looks to

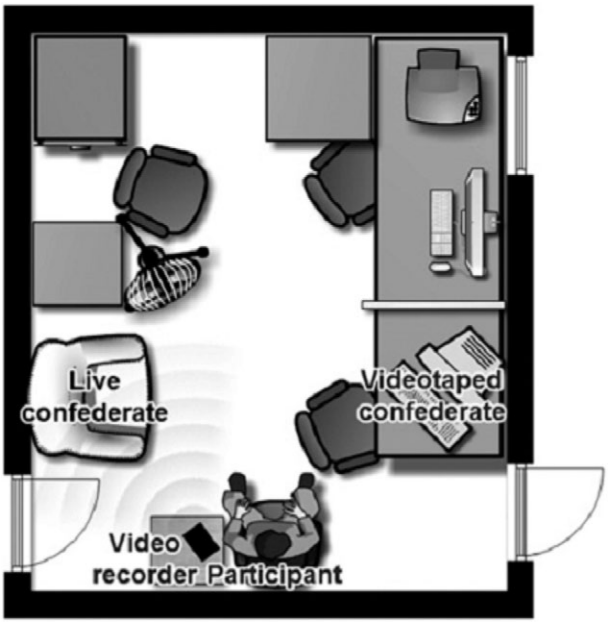

FIGURE 22.6 Participants sat in the middle of the room wearing an eye tracker while either a confederate sat to their left or a videotape of the same confederate played to their right. *Experimental set-up from Laidlaw, K.E.W., Foulsham, T., Kuhn, G., Kingstone, A., 2011. Potential social interactions are important to social attention. Proceedings of the National Academy of Sciences of the United States of America 108, 5548–5553.*

the upper body only), or to the baseline object (for those watching the video, the baseline was the empty chair that the live confederate would have sat in during the alternate condition; for those in the room with the confederate, the baseline was the blank computer screen that would play the video for other participants).

Although participants frequently looked at the videotaped confederate, they seldom turned toward or looked at the live confederate. In fact, relative to the baseline, they were biased not to look at the real confederate. This is precisely the opposite behavior that researchers have observed for images of people—where participants are preferentially biased to look toward the faces of people when they are represented in images (eg, Birmingham et al., 2009; Levy et al., 2012). In sum, these data demonstrate that the mere opportunity for social interaction can profoundly alter social attention, with participants being biased to look away from a stranger.

Converging evidence for this conclusion comes from a series of studies using naturalistic observation (Gallup et al., 2012a,b). For example, Gallup et al. placed an object in a busy hallway and monitored individual's gaze behavior with respect to that object using a hidden camera. The researchers were interested in the extent to which pedestrians would be influenced by the gaze direction of other pedestrians (ie, gaze following). Gallup et al. demonstrated that overall looks toward the object increased when other nearby pedestrians looked toward the object. Interestingly, this depended on which way the participant was facing. When the participant was behind a pedestrian, looks to the object increased. When the participant was facing the pedestrian who gazed at the object, however, participants were actually less likely to look at the object than if no one had looked at the object (ie, the baseline condition). Thus, the gaze of an oncoming pedestrian directed toward a nearby object appeared to inhibit the likelihood of another pedestrian directing their gaze to that object. Recall that this behavior is the opposite of what one would expect given the repeated demonstrations in the laboratory that individuals have a strong (and, some have argued, automatic) tendency to follow the gaze of eyes that are depicted in a schematic face.

Collectively, these studies have demonstrated that in live situations the effect of other people's eyes is the opposite of what would be expected from laboratory experiments, where participants are asked to look at pictures or videos of other people. The underlying principle developed from this work appears to be straightforward: put a participant in a situation where there is a potential cost for looking at someone (eg, engaging in awkward conversation) and people will avoid looking at or following the gaze of other people. Critically, these data suggest that past studies have, at best, grossly overestimated the effect of human eyes and faces on attention as it's realized in more naturalistic environments, and at worst, got it completely backwards.

There is no question from Foulsham et al. (2011), Laidlaw et al. (2011), and Gallup et al. (2012a,b) that in the real world people look less at other people, and less where other people are looking, than laboratory studies would suggest. What is less obvious is whether this represents a general principle of looking behavior in natural situations. Clearly, one possibility is that people always look less at others in a live situation than conventional studies would predict. This is certainly what the data suggest. However, it is worth noting that in the studies by Foulsham, Laidlaw, and Gallup the social norm was not to engage in a social interaction (eg, sitting with a stranger in a waiting room as in Laidlaw et al., 2011). Thus, another possible overarching principle is that it is the normative social context that dictates whether one looks at another person. The studies to date have involved situations where it was simple for people to construe a negative social outcome for engaging with another person (eg, an awkward exchange followed by prolonged silence). Following this reasoning, if one reversed the context to one where engaging in social interaction may be concurrent with social norms rather than opposed, looks toward another person might be enhanced.

To test between these two alternatives, Wu et al. (2013) observed participants' looking behavior in a natural situation, the sharing of a meal, where social interaction would be in line with social norms (ie, a positive consequence of social interaction) rather than opposed to social norms (ie, a negative consequence of social interaction). Volunteers, who were under the impression that the study involved taste perception, were simply asked to sit in a cafeteria setting and eat a prepared salad and answer a questionnaire afterward. They sat in the room either alone, or with another volunteer (dyads). Unbeknownst to them, two hidden cameras were placed in the room, so that their eating behavior could be recorded and their looking behavior measured. In this situation, the social consequences of a social interaction are reversed compared to the context used by Foulsham, Laidlaw, and Gallup. Unlike being in a waiting room, for example, in an eating situation the social norm is to engage in conversation over a meal. Indeed, one would intuitively think there is now a social cost for not engaging in interaction—staring down at your food the entire meal would seem rude. And indeed, as predicted, Wu et al. found an increased preference for participants to look at each other in this situation compared to the data collected in nonsocial situations (eg, looks between dyads were at least twice as great as the looks to the real-life confederate reported by Laidlaw et al., 2011).

These data, when combined with the studies of Foulsham, Laidlaw, and Gallup suggest that the social norms of different contexts will precipitate either negative or positive consequences to engaging in social interaction

and social attention will change correspondingly based on the specific situation. This notion has led us to a new framework for understanding social attention.

The Duality of Eye Gaze

To date we have emphasized that the key difference between being in the presence of a representation of a person (eg, a photo or video), and an actual living person, is that in the former there is no potential for social interaction and in the latter there is. This distinction, as valid as it may be, begs the larger question as to why eye gaze between people is relevant to social interactions.

Our answer to this question began with a consideration of the morphology of the human eye. The human eye's morphology is unique among primates in that it possesses a white sclera surrounding a darker iris and pupil. As a result of this high visual contrast, and unlike nonhuman primates, it is easy to determine where a human being is looking (eg, Anderson et al., 2011). One provocative proposal is that the high contrast polarity of the human eye is an evolutionary adaptation that has facilitated communication between people (Kobayashi and Kohshima, 1997). That is, unlike other primates, humans sacrificed camouflage of their looking behavior for the visibility of communication. As a result we can determine quickly and quietly, and with remarkable fidelity, where someone else is looking and similarly, others can quickly and quietly determine where we are looking. What this means is that human eyes can serve two distinct functions. They can be directed in the environment to acquire information in the world, and they can also be directed to signal information in the world to others. The dual function of gaze was summarized eloquently by Argyle and Cook (1976) when they stated 40 years ago that "Whenever organisms use vision, the eyes become signals as well as channels" (p. xi). In other words, the eyes both gather information (ie, act as a channel) and communicate information to others (ie, act as a signal). This capacity of human gaze to both acquire and signal information is what we refer to as the duality of gaze.

Our hypothesis is that this duality of gaze is critical to the social interactions between individuals that we have been concerned with here, and it is why looking behavior can change so dramatically when people are in the presence of others compared to simply viewing images of others. When people are in the presence of images, their eyes do not signal information, they just acquire it. Thus they are free to look at things that interest them without the additional consideration of what their eye movements might be communicating to someone else. In contrast, when people are in the presence of other people, their eyes acquire *and* signal information, and people need to adjust their looking behavior to accommodate these two, sometimes competing demands.

There are a handful of recent studies that speak directly to this point. One comes from an extension of the original Wu et al. (2013) eating study. In a series of three experiments, Wu et al. (2014) investigated if, and when, humans signal gaze information to other humans while eating. What he found is that there is the general tendency for a person to look away from someone who is about to bite into their food. Critically, this look away is driven by the eater first signaling with their eyes that they are about to open their mouth wide and put food into it. Specifically, what Wu et al. found is that participants are significantly more likely to look down at their food just before taking a bite when they are eating with another person versus when they are eating alone, indicating an awareness of the signaling power of one's own gaze in a social situation. When that signal was conveyed, the other person would then look away from the eater. In short, the Wu et al. study provides the first clear evidence that people use their eyes systematically to signal to others, and that when this is read by another, that signal results in a response behavior that aligns with a situation's social norm (eg, it is rude to look at someone when they open their mouth wide to take a bite and, therefore, the socially appropriate behavior is to look away).

Note again the importance of social norms in looking behavior between individuals, which was first raised in the previous section as a critical factor for whether people did (Wu et al., 2013) or did not look at a stranger (Foulsham et al., 2011; Laidlaw et al., 2011) or follow their gaze (Gallup et al., 2012a,b). A similar normative effect of gaze was also observed in a study by Freeth et al. (2013), where a live or videotaped individual interviewed eye-tracked participants. While looks to the interviewer's face were common in both live and video-taped conditions, when the interviewer made eye contact, participants in the live condition were more likely to look at the face and body of the interviewer than were those in the videotaped condition. In the live condition, participants appeared better able to ascribe the interviewer's eye contact as a signal that accompanied with it a normative response to return that gaze. We argue that not only are people aware of the power of gaze as a signal, as Wu et al. (2014) demonstrate, but that people weigh the benefits and costs associated with signaling one's own attention. The result of this decision often might be contingent on how one's signaling behavior aligns with perceived social norms within a particular social context as defined either by the situation (eg, eating vs. a waiting room) or, as we see next, the very nature of the relationship between two individuals.

In a single simple study, Jarick and Kingstone (2015) demonstrated that the effect of eye contact could be quickly and profoundly altered merely by having participants, who had never met before, play a game in a cooperative or competitive manner. After the game, participants were

asked to make eye contact for a prolonged period of time (10 min), which is well beyond the natural period of a few seconds (Argyle and Dean, 1965). The working hypothesis was that if making eye contact with another person brings into play the duality of eye gaze—that is, gaze serves to both read information from, and signal information to, another person—and that the nature of this gaze communication varies with social context, then requiring people to hold their eye gaze far beyond the comfort zone of a few seconds should serve to amplify the communication that is occurring between individuals to the point that it would be observable in their behavior alone. As shown in Fig. 22.7, this prediction was confirmed.

The cooperative dyads' general behavior, presented on the left of Fig. 22.7, is punctuated by talking, laughing, smiling, and repeated failures to maintain eye contact for sustained periods of time, consistent with the notion that individuals find eye contact uncomfortable and thus they reduce this discomfort by limiting the sending and receiving of (potentially intimate) gaze signals and distract themselves with conversation (eg, Argyle and Dean, 1965). In contrast, the competitive dyads presented on the right of Fig. 22.7, rarely talk, laugh, or even smile, holding direct eye gaze with one another for remarkably long sustained periods of time, with a break in gaze being clearly the exception rather than the rule. This is consistent with the idea that within a competitive context, eye contact could be perceived as a portrayal of dominance (eg, Exline et al., 1965) and thus these participants performed the task as a staring contest. Indeed, some of the participants in the competitive condition did mention the strategy of a staring contest before the eye contact task. In sum, this simple

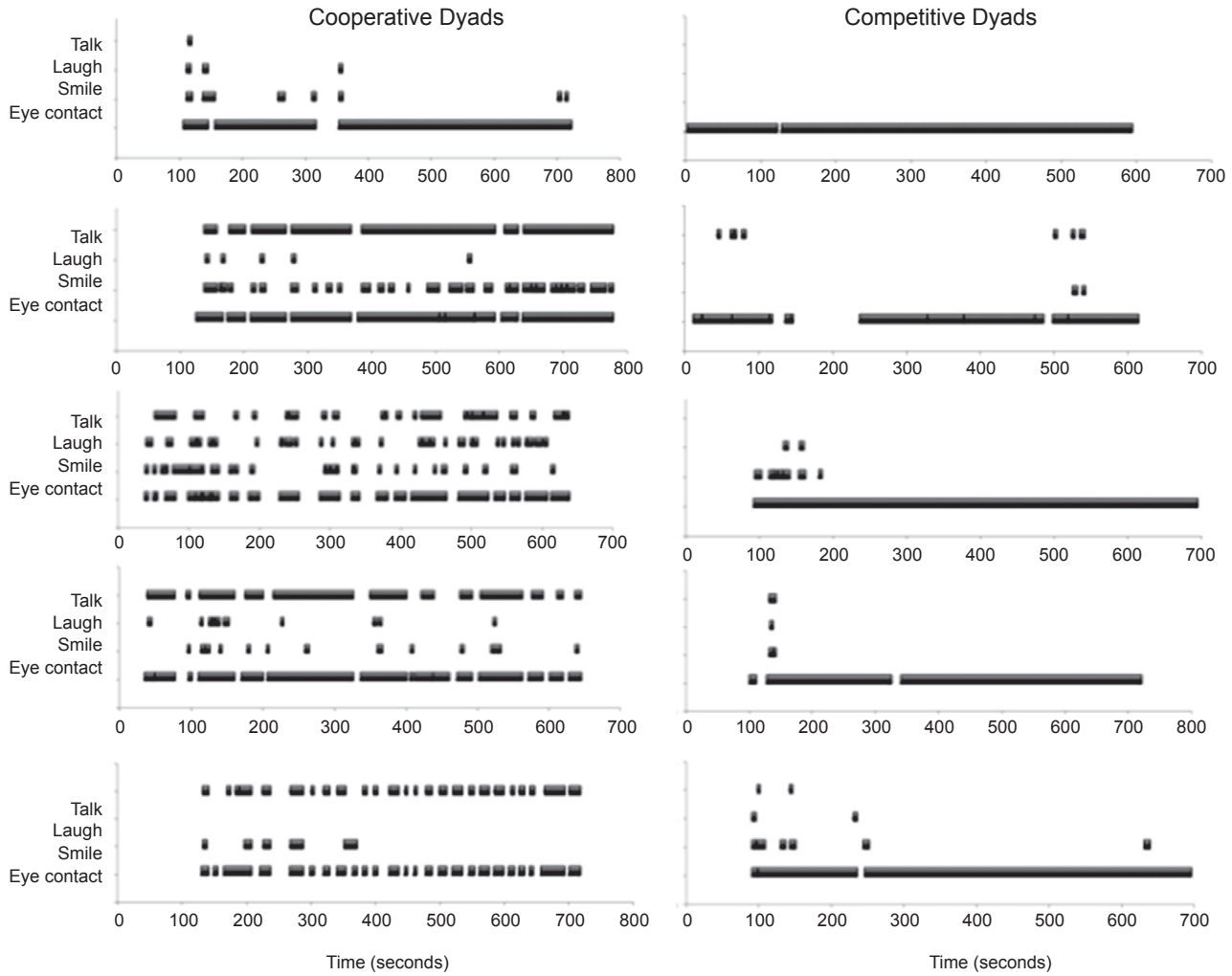

FIGURE 22.7 Scarf plots representing the behavioral markers for five representative dyads in each group who were instructed to maintain sustained eye contact for the total of 10-min period. Note that some dyads total times are longer than 10 min (600 s) due to the subject-driven breaks in between (eg, to rub their eyes, laugh, yawn, stretch, ask a question, etc.). *Adapted with permission from Jarick, M., Kingstone, A., 2015. The duality of gaze: eyes extract and signal social information during sustained cooperative and competitive dyadic gaze. Frontiers in Psychology, 6, 01423. http://dx.doi.org/10.3389/fpsyg.2015.01423.*

study stands as a singular demonstration that when two individuals make eye contact, their gaze serves a communicative function that is exquisitely sensitive to and shaped by small manipulations to the social context that forms their relationship. Just by asking participants to work together on a puzzle for 5 min, either cooperatively or competitively, can profoundly alter their ability to sit side by side and look each other in the eye for a period of time.

Implied Social Presence

In the previous section, we saw how the cognitive ethology approach, which is designed to compare human performance in lab-based and real-world settings, revealed that the consistent and profound bias to fixate and follow the eyes of others that are represented in photos and videos is not replicated in the natural world when the object of one's attention are real people (Foulsham et al., 2011). By taking this initial real-world observation by Foulsham—which you may recall involved individuals walking across campus to buy a treat at a café—back into a more controlled situation, we determined that a critical difference between "lab and life" is that unlike images of people in the lab, in the real-world social attention between individuals is a two-way street, where each person signals as well as reads gaze information. Moreover, we discovered that the nature of this gaze signaling changes with the social context as defined by a situation's normative rules and the relationship between individuals.

One interesting anecdotal finding to emerge when we were first piloting the Foulsham et al. (2011) study was that several people in the lab self-reported that they felt like they were monitoring their looking behavior because they knew that later someone in the lab would see what they had been looking at. Specifically, they felt as if they were being mindful not to look at things that might put them in a "bad light." For instance, they might avoid staring at an attractive person's behind while walking behind them on campus as this might violate a social norm (eg, it is not appropriate to objectify someone by staring at their body). This suggested to us that people were so aware of the duality of their gaze—that it both acquires and signals information—that the receiver of the signal did not need to be physically present to have an impact on where people looked. In short, merely the implication of a social presence (ie, another observer) was sufficient for people to change their looking behavior.

Past work supports the idea that implied social presence might impact behavior (eg, Aiello and Svec, 1993; Putz, 1975). For instance, images of eyes can evoke cooperative behavior in people, augmenting the likelihood of individuals cleaning up litter from cafeteria tables (Ernest-Jones et al., 2011) and even influencing people to increase monetary contributions toward an "honor box" system for consuming drinks (Bateson et al., 2006). Security cameras, which imply the presence of others, also increase prosocial behaviors such that individuals are more likely to provide help to others in a public setting with security cameras versus without (Van Rompay et al., 2009).

Based on these data Risko and Kingstone (2011) entertained the hypothesis that one's awareness of gaze as a signal, combined with the desire to adhere to social norms, might lead people to change their looking behavior when they are aware that their eyes are being monitored. To wit, simply wearing an eye tracker might be sufficient to imply the presence of another individual and alter looking behavior. To test this, volunteers came to the lab and took part in a short sham experiment where they responded to stimuli on a computer while they sat alone in a room with the door closed. Mounted on the wall in this testing room was a sexy swimsuit calendar. After completing the computer task, participants remained alone in the room for a short amount of time. It was participants' looking behavior to the calendar during this free time that was of interest, and the computer task was simply the cover story to allow for the measurement of natural looking behavior toward the calendar.

One group of participants wore an eye tracker that they believed was turned on and recording their gaze. Another group wore an eye tracker that they believed to be turned off. A third group did not wear an eye tracker at all. A hidden camera concealed in the sexy calendar recorded looking behavior, which was later coded offline. The results, illustrated in Fig. 22.8, were unequivocal. If people wore an eye tracker that they believed was turned on, they were disinclined to look at the sexy calendar. If, however, they wore an eye tracker that they believed was turned off,

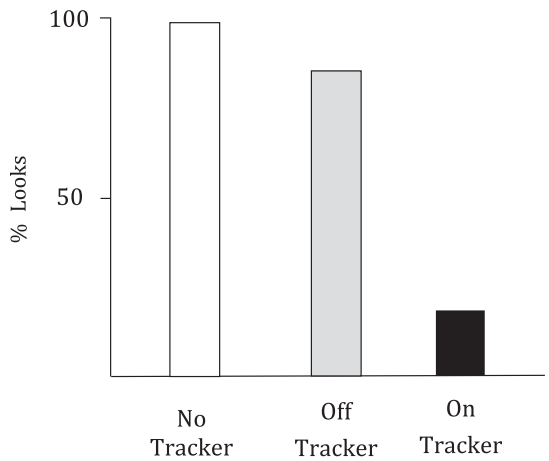

FIGURE 22.8 Percentage of participants who looked at the sexy calendar as a function of whether they wore an eye tracker or not, and whether they believed it to be off or on when being worn. *Adapted with permission from Risko, E.F., Kingstone, A., 2011. Eyes wide shut: implied social presence, eye tracking and attention. Attention, Perception, and Psychophysics 73, 291–296.*

or if were not wearing an eye tracker at all, then they were all too willing to look at the calendar.

This study demonstrates that eye trackers serve as an implied social presence. More importantly, however, it shows that people are so aware of the dual function of their eyes – specifically that they signal as well as acquire information—that merely an implied social presence of another person is sufficient to produce a significant change in looking behavior, with looks conforming to the situation's social norm (eg, it is not appropriate to objectify women). Note that an interesting replication and extension of this finding (Nasiopoulos et al., 2015) suggests that self-monitoring one's looking behavior may be an effortful process. After wearing an active eye tracker for just 10 min participants will revert back to the behavior they would indulge in if they thought no one was watching them (ie, they look at the calendar). Critically, however, the subtlest reminder of the tracker will reactivate the self-monitoring behavior, speaking again to the sensitivity that people have to the dual function of their eyes.

A very clever variation of this implied social presence effect was reported by Gobel et al. (2015). Participants consented to be filmed while they looked at faces of people of different social rank. In the implied presence condition, the participants thought that the actual people whose faces they were looking at would later see their (the participant's) film. In the no social presence condition the participants thought that their film would be stored away and not viewed by anyone. Gobel et al. (2015) predicted that only in the implied social presence condition would participants consider their gaze behavior as a social signal, and this would be evident by their looks conforming to the social norms associated with looking at people of higher or lower rank (de Waal, 1989; Emery, 2000). For instance, in the implied social presence condition, participants would avoid looking at the eyes of higher-ranking individuals. In contrast, in the no social presence condition they would be all too willing to look the high-ranking people in the eyes. This is precisely the pattern of results that Gobel et al. (2015) discovered.

In sum, we have found that natural real-time social attention between individuals is a two-way street, where each person signals as well as reads gaze information (Wu et al., 2014), and that the nature of this gaze signaling changes with the social nature of the relationship between individuals (Jarick and Kingstone, 2015). This duality of gaze is so powerful, and our real-world awareness of it is so strong, that it can have a profound impact on looking behavior even when the person who might receive that signal is not physically present (Richardson and Gobel, 2015; Nasiopoulos et al., 2015; Risko and Kingstone, 2011).

SUMMARY

We began this chapter noting that investigations of human cognition are normally predicated on the assumption that cognitive processes are invariant across different situations. As a result, one can isolate cognitive processes using highly simplified model tasks in controlled lab situations, and apply the findings from those studies to more complex situations. However, we noted that the idea "If A then B" in the lab does not necessarily mean "If A then B" in complex everyday environments. A long-standing challenge to researchers has been how to study human cognition without regressing solely to the simplifying assumption of stability and the resulting use of simplified, highly controlled tasks.

One possible solution is to apply an approach we call cognitive ethology. This chapter has illustrated, with social attention as the vehicle, how by rejecting the assumption of stability, loosening control and accepting the possibility that cognitive processes change across situations, significant scientific insights can be garnered. Specifically, we found that initially when running experiments in the lab using static and video images of people, there was a reliable finding that people looked at the eyes of these images and shifted their attention automatically to where those eyes were directed. The strong prediction was that in real life people look at the eyes and orient attention to where those eyes are directed. Indeed, many researchers have made precisely this claim.

However, a cognitive ethological approach demands that one test these lab-based results against the real world. And it was there that we found patterns of behavior that were contrary to what had been found in the lab. Rather than looking at faces of real people as they approached, people looked away (Foulsham et al., 2011); and rather than looking at the locations that people were directing their eyes, observers looked away when they thought their own actions were also observable by those people (Gallup et al., 2012a,b). This gave rise to the hypothesis that what was going on in the real world, and what had been lacking in the lab, was the fact that in everyday, dynamic environments, eyes both take in and signal information to others. That is, eyes serve a communicative function of receiving and sending information. In contrast, when looking at images, one's eyes just take in information.

With this real world behavior in place, and the duality of gaze concept advanced, we returned to the lab to investigate the hypothesis while always being on one's guard that the real-world effect may be altered when it is moved into a more controlled setting. The results of these investigations have given strong support to the duality of gaze hypothesis (Risko et al., 2016). They also raised the possibility that the communicative function of gaze is so pronounced that even an implied social presence is enough

to impact looking behavior, a prediction that has been given a ringing endorsement (Gobel et al., 2015; Nasiopoulos et al., 2015; Risko and Kingstone, 2011).

Before closing, we would be remiss if we did not acknowledge that we are not the only individuals to raise serious concerns with the external validity and real world value of simplified and controlled lab-based investigations of human cognition. In what follows, we briefly consider how our cognitive ethology approach is similar to and distinct from other frameworks.

The Ethological Approach

As the name of our cognitive ethology approach suggests, it is in some ways similar to the ethological approach, which gained prominence during the 1960s (eg, Carthy, 1966; see Hutt and Hutt, 1970 for a review). Ethology focuses on describing behavior patterns of humans and animals in their natural contexts. Our approach and the classic ethological approach are similar in that they both seek to provide a detailed description of behavior as organisms interact within their natural environment. Furthermore, both approaches consider it essential that natural behavior be observed and described as it normally occurs rather than being modified or probed in overly controlled settings.

There are, however, several critical differences between the two approaches. The primary difference is that, in our cognitive ethology approach, as implied by the term "cognitive," the aim is to relate the observations to classically cognitive concepts such as attention. Our approach views these concepts as being contextualized processes revealed by the interaction of an individual with their environment. In contrast, classical ethology was concerned mainly with overt behavior and did not seek to draw inferences about cognition.

The Ecological Approach

Our approach is also similar to the ecological approach developed during the 1950s and 1960s (eg, Barker and Wright, 1955; Wright, 1967; see Hutt and Hutt, 1970 for a review). The ecological approach focuses on characterizing the situations (ie, "habitats") in which people behave by observing and describing behavior and seeks to understand how the environment (ie, "habitat") relates to or determines the latter. The primary similarity between this and our approach is the assumption that characterizing situations is necessary for understanding human behavior.

However, cognitive ethology differs from the ecological approach in important ways. First, the approaches differ with regard to emphasis or relative importance of the environment and individual. While the ecological approach places primary emphasis on the habitat, our approach does require the importance of the habitat to overshadow the individual. Second, the approaches differ with respect to the way they treat subjective reports and personal insights of the participants in the studies. Though the ecological approach allowed for considerably more discussion of peoples' mental states than the original ethological approach, particularly those pertaining to the goals of their behaviors (Wright, 1967), the ecological approach nevertheless focused on inferring such mental states from observable behaviors. In other words, subjective reports are not a valid method for inferring mental states within the ecological approach.

In contrast, cognitive ethology considers subjective reports and personal insights into one's performance as providing critical and informative data that must be accounted for and incorporated into theories and explanations. Indeed, combining objective data and subjective reports is at the heart of this approach. An excellent example is how the anecdotal evidence that people felt like they were controlling their looking behavior while wearing an eye tracker during the pilot study of Foulsham et al. (2011) resulted in a line of research regarding the duality of gaze and implied social presence (eg, Risko and Kingstone, 2011; Nasiopoulos et al., 2015).

Ecological Optics

The central idea of Gibson's theory (1950, 1979) is that perception is driven by the structure of the environment. The Gibsonian formula is "perception is a function of stimulation and stimulation is a function of the environment" (Gibson, 1959, p. 459); therefore, perception is a function of the environment. The theory is ecological because it puts a strong emphasis on the environment, much like the "habitat" in the ecological approach described earlier.

There are several similarities between Gibson's approach and cognitive ethology. The first is the idea that individuals are embedded in an environment and that cognitive concepts cannot be understood as being independent of that environment. The second involves rejection of the assumption of process stability. Gibson keenly observed that "the stimulation of receptors and the presumed sensations . . . are variable and changing in the extreme, unless they are controlled in the laboratory" (Gibson, 1966, p. 3). Thus the focus is on naturally occurring variability rather than variability that is manipulated or created in the laboratory.

But there are also important differences. Gibson's framework emphasizes the environment, and little consideration is given to the individual, whereas cognitive ethology places an equal emphasis on both. Second, the ultimate goal of Gibson's framework is to derive perception–action laws "of the most basic and general kind" (Turvey, 1992, p. 86). In contrast, cognitive ethology

focuses on describing situations, though general principles might emerge across different situations (eg, the duality of gaze (or lack thereof) and situational norms as being a primary determinant of looking behavior).

Neisser's Ecological Validity

We enthusiastically agree with Neisser's (1976) statement that "a satisfactory theory of human cognition can hardly be established by experiments that provide inexperienced subjects with brief opportunities to perform novel and meaningless tasks" (p. 8). Yet, while Neisser articulated eloquently the need for more ecological validity, he did not specify a systematic approach for attaining that ecological goal. Our formulation of the cognitive ethology approach articulates the assumptions and principles that must be applied in order to attain ecological validity. In other words, whereas Neisser outlined the problem in the field, we believe that we have outlined an approach that goes a long way toward providing a solution to this problem (see in detail Kingstone et al., 2008).

CONCLUDING COMMENTS

We follow in the footsteps of William James, Ulrich Neisser, and others in arguing that the goal of cognitive research is to understand how attention operates in the real world and that controlled laboratory studies alone are inadequate for the task. We suggest that controlled laboratory investigations, and natural real world investigations, are founded on different principles and each complements the other. That complementary relationship was highlighted in the present chapter and through the investigation of social attention. Lab-based findings and principles (gaze selection and following) were found wanting when natural behavior was observed; but the ideas to emerge (the duality of gaze) were tested (and continue to be tested) using controlled experimentation. By moving between levels of investigation and being aware of what principles are underlying the research being conducted, we believe that the cognitive ethology research approach has the potential to enable researchers to reach their ultimate goal of understanding human cognition as it operates across levels of complexity, and ultimately, in everyday life.

REFERENCES

Aiello, J.R., Svec, C.M., 1993. Computer monitoring of work performance: extending the social facilitation framework to electronic presence. Journal of Applied Social Psychology 23, 537–548.

Akiyama, T., Kato, M., Muramatsu, T., Saito, F., Umeda, S., Kashima, H., 2006. Gaze but not arrows: a dissociative impairment after right superior temporal gyrus damage. Neuropsychologia 44, 1804–1810.

Anderson, N., Risko, E.F., Kingstone, A., 2011. Exploiting human sensitivity to gaze for tracking the eyes. Behavior Research Methods 43, 843–852.

Andrews, T.J., Davies-Thompson, J., Kingstone, A., Young, A.W., 2010. Internal and external features of the face are represented holistically in face-selective regions of visual cortex. Journal of Neuroscience 30, 3544–3552.

Argyle, M., Cook, M., 1976. Gaze and Mutual Gaze. Cambridge University Press, Cambridge, UK.

Argyle, M., Dean, J., 1965. Eye-contact, distance and affiliation. Sociometry 28, 289–304.

Aydede, M., Robbins, P. (Eds.), 2009. The Cambridge Handbook of Situated Cognition. Cambridge University Press, New York, NY.

Ballard, D.H., Hayhoe, M.M., 2009. Modeling the role of task in the control of gaze. Visual Cognition 17, 1185–1204.

Ballard, D.H., Hayhoe, M.M., Pelz, J.B., 1995. Memory representations in natural tasks. Journal of Cognitive Neuroscience 71, 66–80.

Barker, R.G., Wright, H.F., 1955. Midwest and Its Children: The Psychological Ecology of an American Town. Harper and Row, New York.

Bateson, M., Nettle, D., Roberts, G., 2006. Cues of being watched enhance cooperation in a real-world setting. Biology Letters 2, 412–414.

Bindemann, M., Scheepers, C., Burton, A.M., 2009. Viewpoint and center of gravity affect eye movements to human faces. Journal of Vision 9, 1–16.

Birmingham, E., Bischof, W.F., Kingstone, A., 2008a. Social attention and real world scenes: the roles of action, competition, and social content. Quarterly Journal of Experimental Psychology 61, 986–998.

Birmingham, E., Bischof, W.F., Kingstone, A., 2008b. Gaze selection in complex social scenes. Visual Cognition 16, 341–355.

Birmingham, E., Bischof, W.F., Kingstone, A., 2009. Saliency does not account for fixations to eyes within social scenes. Vision Research 49, 2992–3000.

Birmingham, E., Kingstone, A., 2009. Human social attention: a new look at past, present and future investigations. Annals of the New York Academy of Sciences 1156, 118–140.

Broadbent, D.E., 1971. Decision and Stress. Academic Press, London.

Broadbent, D.E., 1991. A word before leaving. In: Meyer, D.E., Kornblum, S. (Eds.), Attention and Performance, vol. XIV. Bradford Books/MIT Press, Cambridge, MA, pp. 863–879.

Calder, A.J., Beaver, J.D., Winston, J.S., Dolan, R.J., Jenkins, R., Eger, E., Henson, R.N.A., 2007. Separate coding of different gaze directions in the superior temporal sulcus and inferior parietal lobule. Current Biology 17, 20–25.

Campbell, R., Heywood, C.A., Cowey, A., Regard, M., Landis, T., 1990. Sensitivity to eye gaze in prosopagnosic patients and monkeys with superior temporal sulcus ablation. Neuropsychologia 28, 1123–1142.

Carrasco, M., 2011. Visual attention: the past 25 years. Vision Research 5113, 1484–1525.

Carthy, J.D., 1966. The Study of Behavior. William Clowes and Sons, London.

Cheng, J.T., Tracey, J.L., Foulsham, T., Kingstone, A., Henrich, J., 2013. Two ways to the top: evidence that dominance and prestige are distinct yet viable avenues to social rank and influence. Journal of Personality and Social Psychology 104, 103–125.

Coutrot, A., Guyader, N., 2014. How saliency, faces, and sound influence gaze in dynamic social scenes. Journal of Vision 14 (5), 1–17.

Deaner, R.O., Platt, M.P., 2003. Reflexive social attention in monkeys and humans. Current Biology 13, 1609–1613.

Driver, J., Davis, G., Ricciardelli, P., Kidd, P., Maxwell, E., Baron-Cohen, S., 1999. Gaze perception triggers visuospatial orienting by adults in a reflexive manner. Visual Cognition 6, 509–540.

Emery, N.J., 2000. The eyes have it: the neuroethology, function and evolution of social gaze. Neuroscience & Biobehavioral Review 24, 581–604.

Ernest-Jones, M., Nettle, D., Bateson, M., 2011. Effects of eye images on everyday cooperative behavior: a field experiment. Evolution and Human Behavior 323, 172–178.

Exline, R.V., Gray, D., Schuette, D., 1965. Visual behaviour in a dyad as affected by interview content and sex of respondent. In: Tomkins, S., Izzard, C. (Eds.), Affect, Cognition and Personality. Springer Publishing, New York.

Foulsham, T., Underwood, G., 2007. How does the purpose of inspection influence the potency of visual salience in scene perception? Perception 36, 1123–1138.

Foulsham, T., Underwood, G., 2008. What can saliency models predict about eye movements? Spatial and sequential aspects of fixations during encoding and recognition. Journal of Vision 82, 1–17.

Foulsham, T., Cheng, J.T., Tracy, J.L., Henrich, J., Kingstone, A., 2010. Gaze allocation in a dynamic situation: effects of social status and speaking. Cognition 117, 319–331.

Foulsham, T., Walker, E., Kingstone, A., 2011. The where, what and when of gaze allocation in the lab and the natural environment. Vision Research 5117, 1920–1931.

Foulsham, T., Sanderson, L.A., 2013. Look who's talking? Sound changes gaze behaviour in a dynamic social scene. Visual Cognition 21, 922–944.

Freeth, M., Foulsham, T., Kingstone, A., 2013. What affects social attention? Social presence, eye contact and autistic traits. PLoS One 81, e53286. http://dx.doi.org/10.1371/journal.pone.0053286.

Friesen, C.K., Kingstone, A., 1998. The eyes have it!: reflexive orienting is triggered by nonpredictive gaze. Psychonomic Bulletin & Review 5, 490–495.

Friesen, C.K., Ristic, J., Kingstone, A., 2004. Attentional effects of counterpredictive gaze and arrow cues. Journal of Experimental Psychology: Human Perception & Performance 30, 319–329.

Gallup, A.C., Chong, A., Couzin, I.D., 2012a. The directional flow of visual information transfer between pedestrians. Biology Letters 8, 520–522.

Gallup, A.C., Hale, J.J., Sumpter, D.J.T., Garnier, S., Kacelnik, A., Krebs, J.R., Couzin, I.D., 2012b. Visual attention and the acquisition of information in human crowds. Proceedings of the National Academy of Sciences of the United States of America 109, 7245–7250.

Gobel, M.S., Kim, H.S., Richardson, D.C., 2015. The dual function of social gaze. Cognition 136, 359–364.

Gibson, J.J., 1950. The Perception of the Visual World. Houghton Mifflin, Boston, MA.

Gibson, J.J., 1959. Perception as a function of stimulation. In: Koch, S. (Ed.), Psychology: A Study of Science, Study I. Conceptual and Systematic, Sensory, Perceptual and Physiological Formulations, vol. 1. McGraw-Hill Book Company, New York, pp. 456–501.

Gibson, J.J., 1966. The Senses Considered as Perceptual Systems. Houghton Mifflin, Boston, MA.

Gibson, J.J., 1979. The Ecological Approach to Visual Perception. Houghton Mifflin, Boston, MA.

Glenberg, A.M., 2010. Embodiment as a unifying perspective for psychology. Wiley Interdisciplinary Reviews: Cognitive Science 14, 586–596.

Hayhoe, M., Ballard, D., 2005. Eye movements in natural behavior. Trends in Cognitive Science 9, 188–194.

Henderson, J.M., Williams, C.C., Falk, R., 2005. Eye movements are functional during face learning. Memory & Cognition 33, 98–106.

Heywood, C.A., Cowey, A., Rolls, E.T., 1992. The role of the face cell area in the discrimination and recognition of faces by monkeys. Philosophical Transactions of the Royal Society B 335, 31–38.

Hoffman, E.A., Haxby, J.V., 2000. Distinct representations of eye gaze and identity in the distributed human neural system for face perception. Nature Neuroscience 3, 80–84.

Hollan, J., Hutchins, E., Kirsh, D., 2000. Distributed cognition: toward a new foundation for human-computer interaction research. ACM Transactions on Computer-Human Interaction (TOCHI) 72, 174–196.

Hutchins, E., 1995. Cognition in the Wild. MIT Press, Cambridge, MA.

Hutt, S.J., Hutt, C., 1970. Direct Observation and Measurement of Behavior. Charles C. Thomas Publisher, Springfield, IL.

Itti, L., Koch, C., 2000. A saliency-based search mechanism for overt and covert shifts of visual attention. Vision Research 40, 1489–1506.

Jarick, M., Kingstone, A., 2015. The duality of gaze: eyes extract and signal social information during sustained cooperative and competitive dyadic gaze. Frontiers in Psychology 6 (01423). http://dx.doi.org/10.3389/fpsyg.2015.01423.

Jonides, J., 1981. Voluntary versus automatic control over the mind's eye's movement. In: Long, J.B., Baddeley, A.D. (Eds.), Attention and Performance, vol. IX. Erlbaum, Hillsdale, NJ, pp. 187–203.

Killeen, P.R., Glenberg, A.M., 2010. Resituating cognition. Comparative Cognition & Behavior Reviews 5, 59–77.

Kingstone, A., 2009. Taking a real look at social attention. Current Opinion in Neurobiology 19, 52–56.

Kingstone, A., Smilek, D., Ristic, J., Friesen, C.K., Eastwood, J.D., 2003. Attention, researchers! It is time to take a look at the real world. Current Directions in Psychological Science 12, 176–180.

Kingstone, A., Smilek, D., Eastwood, J.D., 2008. Cognitive Ethology: a new approach for studying human cognition. British Journal of Psychology 99, 317–345.

Kingstone, A., Tipper, C., Ristic, J., Ngan, E., 2004. The eyes have it!: an fMRI investigation. Brain & Cognition 55, 269–271.

Klein, R.M., 2000. Inhibition of return. Trends in Cognitive Sciences 44, 138–147.

Kobayashi, H., Kohshima, S., 1997. Unique morphology of the human eye. Nature 387, 767–768.

Laidlaw, K.E.W., Foulsham, T., Kuhn, G., Kingstone, A., 2011. Potential social interactions are important to social attention. Proceedings of the National Academy of Sciences of the United States of America 108, 5548–5553.

Laidlaw, K.E.W., Risko, E.F., Kingstone, A., 2012. A new look at social attention: orienting to the eyes is not entirely under volitional control. Journal of Experimental Psychology: Human Perception & Performance 38, 1132–1143.

Land, M.F., Hayhoe, M., 2001. In what ways do eye movements contribute to everyday activities? Vision Research 4125, 3559–3565.

Langton, S.R.H., Bruce, V., 1999. Reflexive social orienting. Visual Cognition 6, 541–567.

Land, M.F., Lee, D.N., 1994. Where we look when we steer. Nature 369, 742–744.

Land, M.F., McLeod, P., 2000. From eye movements to actions: how batsman hit the ball. Nature Neuroscience 3, 1340–1345.

Levy, J., Foulsham, T., Kingstone, A., 2012. Monsters are people too. Biology Letter 9. http://dx.doi.org/10.1098/rsbl.2012.0850.

Nasiopoulos, E., Risko, E.F., Foulsham, T., Kingstone, A., 2015. Wearable computing: will it make people prosocial? British Journal of Psychology 106, 209–216.

Neisser, U., 1976. Cognition and Reality. Freeman, San Francisco, CA.

Olk, B., Cameron, B., Kingstone, A., 2008. Enhanced orienting effects: evidence for an interaction principle. Visual Cognition 16, 979–1000.

Olk, B., Hildebrandt, H., Kingstone, A., 2010. Involuntary but not voluntary orienting contributes to a disengage deficit in visual neglect. Cortex 46, 1149–1164.

Olk, B., Kingstone, A., 2015. Attention and aging: measuring effects of involuntary and voluntary orienting in isolation and in combination. British Journal of Psychology 106, 235–252.

Pelphrey, K.A., Sasson, N.J., Reznick, J.S., Paul, G., Goldman, B.D., Piven, J., 2002. Visual scanning of faces in autism. Journal of Autism and Developmental Disorders 32, 249–261.

Posner, M.I., 1978. Chronometric Explorations of Mind. Erlbaum, Hillsdale, NJ.

Posner, M.I., 1980. Attention and the detection of signals. Journal of Experimental Psychology: General 109, 160–174.

Putz, V.R., 1975. The effects of different modes of supervision on vigilance behaviour. British Journal of Psychology 66, 157–160.

Richardson, D.C., Gobel, M.S., 2015. Social attention. In: Fawcett, J., Risko, E., Kingstone, A. (Eds.), The Handbook of Attention. MIT Press, Cambridge, MA.

Risko, E.F., Kingstone, A., 2011. Eyes wide shut: implied social presence, eye tracking and attention. Attention, Perception, and Psychophysics 73, 291–296.

Risko, E.F., Richardson, D.C., Kingstone, A., 2016. Breaking the fourth wall of cognitive science: real world social attention and the dual function of gaze. Current Directions in Psychological Science 25, 70–74.

Ristic, J., Wright, A., Kingstone, A., 2007. Attentional control and reflexive orienting to gaze and arrow cues. Psychonomic Bulletin and Review 14, 964–969.

Ristic, J., Kingstone, A., 2006. Attention to arrows: pointing to a new direction. Quarterly Journal of Experimental Psychology 59, 1921–1930.

Ristic, J., Kingstone, A., 2009. Rethinking attentional development: reflexive and volitional orienting in children and adults. Developmental Science 12, 289–296.

Ristic, J., Kingstone, A., 2012. A new form of human spatial attention: automated symbolic orienting. Visual Cognition 20, 244–264.

Van Rompay, T.J., Vonk, D.J., Fransen, M.L., 2009. The eye of the camera effects of security cameras on prosocial behavior. Environment and Behavior 41, 60–74.

Smilek, D., Enns, J.T., Eastwood, J.D., Merikle, P.M., 2006. Relax! Cognitive style influences visual search. Visual Cognition 14, 543–564.

Turvey, M.T., 1992. Ecological foundations of cognition. In: Pick Jr., H.L., van den Broek, P., Knill, D.C. (Eds.), Cognition: Conceptual and Methodological Issues. APA, Washington, DC, pp. 85–117.

de Waal, F.B.M., 1989. Chimpanzee Politics: Power and Sex Among Apes. John Hopkins University Press, Baltimore, MD.

Walker-Smith, G., Gale, A.G., Findlay, J.M., 1977. Eye movement strategies involved in face perception. Perception 6, 313–326.

Wilson, M., 2002. Six views of embodied cognition. Psychonomic Bulletin & Review 9, 625–636.

Wright, H.F., 1967. Recording and Analyzing Child Behavior with Ecological Data from an American Town. Harper and Row, New York.

Wu, D.W.-L., Bischof, W.F., Kingstone, A., 2013. Looking while eating: the importance of social context to social attention. Scientific Reports 3, 2356. http://dx.doi.org/10.1038/srep02356.

Wu, D.W.-L., Bischof, W.F., Kingstone, A., 2014. Natural gaze signaling in a social context. Evolution & Human Behavior 35, 211–218.

Yarbus, A.L., 1967. Eye Movements and Vision (B. Haigh, Trans.). Plenum Press, New York. Original work published 1965.

Yovel, G., Kanwisher, N., 2005. The neural basis of the behavioral face-inversion effect. Current Biology 15, 2256–2262.

Chapter 23

Human Sociobiology and Group Selection Theory

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WHAT IS HUMAN SOCIOBIOLOGY?

Human sociobiology is an academic discipline whose practitioners employ what has been called the adaptationist program (Gould and Lewontin, 1979) to explore the evolutionary basis of human social behavior. The adaptationist approach is one in which researchers use Darwinian natural selection theory to advance and test hypotheses on the possible adaptive (ie, reproductive) value of a particular behavioral trait (Alcock, 2001). So, for example, the observation that men appear to be selective in their choice of mates leads to the adaptationist prediction that men will find young women at peak fertility more attractive than women who are older. Female fertility peaks in the mid-twenties and declines rapidly, especially after age 35 (Menkin et al., 1986). This prediction can be checked in many ways, such as by examining the age at marriage of men and their partners. As expected, men from many cultures typically marry women who are younger than they are (Buss, 1989) and so should succeed in having more offspring overall on average than men who marry women who are older, which as predicted, rarely occurs. (According to census data from the United States only about 14% of all wives are two years or older than their spouses; see http://economix.blogs.nytimes.com/2013/04/01/on-whether-women-can-or-do-marry-younger-men/.) The mating preferences of men and women, an important aspect of our social behavior, has been subjected to intensive analysis by persons aware of Darwinian selection with generally supportive results (Buss, 2013; Buss and Schmidt, 1993; Kenrick, 2011).

Human sociobiology can be said to be similar, if not identical, to other evolutionary subdisciplines that also are founded on natural selection theory, especially evolutionary psychology, evolutionary anthropology and human behavioral ecology (Daly and Wilson, 1999). True, there are some differences between, say, human behavioral ecology and evolutionary psychology, as in the emphasis in the first discipline on measuring the current reproductive success of individuals exhibiting a putative behavioral adaptation versus demonstrating that a psychological trait appears to be designed to solve a reproductive problem that would have confronted our ancestors, a major goal of evolutionary psychologists (Smith et al., 2001). Even so, all these academic disciplines can be accommodated under the umbrella of behavioral ecology: the discipline that employs adaptationism in the study of the behavior of all living things in relation to their environment. The distinctive feature of human sociobiology and allied disciplines is the focus on a single organism, the human species, but the research approach that underlies all these fields is essentially the same as that applied to the behavioral ecology of creatures as different as slime molds, parasitic plants, and prairie voles, to name a few.

THE FIRST WAVE OF CRITICISMS OF SOCIOBIOLOGY

Despite the broad-based nature of the adaptationist program and its long use by researchers, persons applying this approach to the study of human behavior have come under fire from their fellow academics. E.O. Wilson (1994) was immediately attacked, verbally and physically, by persons who strongly disapproved of the human component to the field of sociobiology that he named in 1975. His colleagues, Stephen Jay Gould and Richard Lewontin, were prominent among those who vehemently disparaged the discipline and Wilson: “These [discredited early ‘evolutionary’] theories provided an important basis for the

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00023-5

enactment of sterilization laws and restrictive immigration laws by the United States between 1910 and 1930 and also for the eugenics policies which led to the establishment of gas chambers in Nazi Germany. The latest attempt to reinvigorate these tired theories comes with the alleged creation of a new discipline, sociobiology" (Allen et al., 1975).

Subsequent to the initial attacks on sociobiology, Gould and Lewontin (1979) wrote an extremely influential article (over 2500 citations as of late 2013) in which they criticized the entire adaptationist program on various grounds, but especially because adaptationists supposedly did not follow scientific principles in their work and instead accepted hypotheses ("just so stories" in Gould and Lewontin's labeling) without testing them. Similarly, evolutionary psychologists have come in for their share of criticism and then some (Buller, 2005; Ehrlich, 2000; Gannon, 2002; Rose and Rose, 2000).

Needless to say, these criticisms did not go unnoticed by sociobiologists and others who employ the adaptationist program (Alcock, 2001; Buss and Haselton, 2005; Hagen, 2005; Kenrick, 1995). Among the responses given by adherents of adaptationism was the point that "just so story" is merely another, albeit disparaging, name for a possible explanation (or hypothesis) and that sociobiological journals have always published articles that present data designed to test hypotheses to determine if they are likely to be true or false. In this the sociobiologist is no different from any other scientist.

The advocates of sociobiology have also pointed out that many of the critiques of the field are based on a failure to understand the difference between explanation and justification. All scientific research is aimed at explaining something, not justifying the characteristic under investigation. If a human sociobiologist concludes that it is adaptive for men to behave in ways that increase their chances of copulating with highly fertile women, the researcher is not arguing that this aspect of male behavior is morally or socially desirable. Instead the researcher is attempting to understand why men behave the way they do, not to justify what may well lead individuals to engage in immoral or socially damaging behavior. The difference between explanation and justification is easily understood when the subject organism is a slime mold or elephant seal, but critics of the application of evolutionary theory to human behavior often either fail to grasp the distinction or try to blur it so as to paint the adaptationist as an apologist for actions that most people consider wrong.

The human sociobiologist approaches human social behavior in the same way that behavioral ecologists and other evolutionary researchers study the possible adaptive value of the behavior of slime molds and elephant seals. If this approach, based on natural selection theory, works for slime molds and elephant seals, then why not tackle human behavior in the same way? We are an animal species. Our gametes have DNA in them. When individuals attempt to reproduce, their special DNA may or may not be passed on to the next generation. Because natural selection must have acted on human genetic variation in the past, we can expect humans to behave in ways today that would have promoted the transmission of those forms of genes that were associated with reproductive success in the past. This is a potentially testable proposition. If wrong, suitable tests will reveal the error made by the human sociobiologist or evolutionary psychologist.

Most evolutionary biologists, a subset of psychologists and a number of sociologists have considered and rejected the early criticisms of the application of adaptationism to the study of human behavior (eg, Confer et al., 2010). Despite the barrage of such criticism that sociobiologists faced in the 1970s and 1980s, and that evolutionary psychologists have had to cope with more recently, these fields are flourishing. For example, both in textbooks and in a major psychology journal, there have been substantial increases in the number of articles on evolutionary psychology in recent years (Webster, 2007; see also http://bit.ly/KZAaZw). Although there may still be pockets of resistance, perhaps especially among the social sciences, it is fair to say that the adaptationist approach has carried the day (Alcock, 2001; Dunbar and Barrett, 2007; Lopreato and Crippen, 1999). I shall now focus on another kind of argument that has been and continues to be raised against the adaptationist approach to humans (and other species). I speak of the claim that some evolutionists have improperly ignored an important novel theoretical approach, one based on the occurrence of "multilevel" selection. Acceptance of this approach would, according to its adherents, require a major reevaluation of the adaptive basis of social behavior, including that of humans.

KIN SELECTION AND HUMAN SOCIOBIOLOGY

When developing hypotheses on the behavior of humans and other animals, adaptationists have, as noted earlier, usually tried to explain why a given behavior might contribute to the reproductive success of individuals of the species under examination. This approach has been productive inasmuch as tests of particular adaptive value hypotheses have often led researchers to conclude that the evolved function of the trait is indeed to help individuals reproduce successfully in an unconscious competition with other members of their species. For example, the male desire to copulate with and marry young women as opposed to older ones generally leads men to seek out highly fertile partners as opposed to less fertile ones. The result: a greater chance of partner pregnancies and greater lifetime reproductive success for the men so motivated.

There are cases in which animals appear to give up chances to reproduce personally in favor of helping others in ways that might well boost the reproductive output of the helped individuals. These cases, needless to say, create problems for the adaptationist. How could cooperative behavior of this sort persist in populations subject to natural selection? And cases of self-sacrificing behavior are not all that uncommon in the animal kingdom in general, including the human species. The evolutionary biologist W.D. Hamilton (1964) is usually credited with a solution to the puzzle that has become widely accepted, a solution that rests upon an amended version of natural selection theory usually called kin selection or inclusive fitness theory. According to this theory, the ultimate *unconscious* goal of individuals is not really to reproduce personally more than others of their species but to pass on more of their genes to the next generation than their "rivals." The direct way to make a genetic contribution to the next generation is to have an offspring that survives long enough to also reproduce. The parent donates genes to its offspring and these may have a chance to be copied and transmitted in the next generation. Only genes that make it from one generation to the next can influence the development of individuals in the next generation.

But in addition to the direct contribution of genes via personal reproduction, individuals might in some instances help genetically similar others to reproduce, in which case the helpful altruist might contribute to passing on the genes it shares with the individual it helped. Relatives share genes in common (thanks to shared ancestors) and therefore an organism that gives up a chance to reproduce personally could conceivably pass on more of its genes by boosting the reproductive success of a relative. What is required is that the helped relative increase its reproduction sufficiently to more than compensate the helper for its loss of personal reproduction. Kin selection has its effect, like natural selection, via selection at the level of the gene. Kin selection can lead to changes in gene frequencies that arise as a result of relatives helping (or harming) each other in ways that affect the opportunities for transmission of their special DNA to the next generation.

Hamilton realized that the indirect route to genetic propagations was just another way for an individual to help pass his or her genes into the future, the sum total of which constituted that individual's inclusive fitness (direct fitness plus indirect fitness). This insight was greatly appreciated by behavioral ecologists, including human sociobiologists, who saw that they had a possible explanation for the evolution of otherwise puzzling behaviors, namely helpful self-sacrificing actions whose cost in loss of direct fitness could be demonstrated to be less than the gain in indirect fitness, leading to an overall increase in that individual's inclusive fitness.

As others have pointed out (Gardner et al., 2011), Darwin anticipated Hamilton's solution even though he, Darwin, knew nothing about genes. But he did know that cattle breeders could select for desirable traits in cattle by breeding the relatives of those individuals with the characteristics (eg, densely muscled, meaty bodies) that they wanted to see in the next generation of beef cows (Darwin, 1859). Hamilton had the benefit of being a 20th century biologist for whom the concept of genes was familiar. Because he realized that the genetic currency of selection was the same whether individuals reproduced personally or helped their relatives reproduce, he made the inclusive fitness breakthrough.

GROUP SELECTION AND HUMAN ALTRUISM

David Sloan Wilson (1975) and co-authors (eg, (2008)) have for many years now made the case that adaptationists are far too narrowly focused on the theory of evolution by natural selection at the level of the individual. It is not enough, they argue, to have natural selection acting on differences in reproductive success at the individual level and kin selection acting on differences in the indirect fitness of individuals that help relatives reproduce. For multilevel selectionists, selection can act at the level of the gene, the individual, *and* the group. According to these theorists, there are some behavioral attributes, especially cooperation and altruism among individuals, that cannot be fully explained without reference to the group selectionist component of multilevel selection, namely selection that acts on differences in the genetic success of entire groups of individuals.

For adaptationists using inclusive fitness theory, evolution could have been shaped by natural selection acting on reproductive differences among individuals within groups and by kin selection acting on differences among individuals in their effects on the reproductive success of genetically similar others. In contrast, D.S. Wilson's multilevel selection theory involves two components of selection, one occurring within groups and another occurring between groups, each with their own effects on the transmission of genes to the next generation. However, as Reeve (2000) and others (eg, West et al., 2011) make clear, inclusive fitness theory and multilevel theory are merely different ways in which to cut up the same genetic pie because in the last analysis evolution occurs only when the processes of selection change the frequency of genes within populations. According to Reeve (2000), "That is essentially *all* there is to the mathematical relationship between inclusive fitness and multi-level selection models—they are essentially equivalent, their only differences being definitional." For example, group selectionists treat groups composed of relatives in terms of their total genetic contributions to the next generation whereas inclusive fitness theorists treat family groups as an aggregation of

individuals, each with its own genetic success. However, Wilson and his colleagues have insisted that despite the mathematical equivalence of inclusive fitness theory and multilevel theory, their version of group selection is essential for a proper analysis of the evolution of cooperation.

WHY HAVE WILSON'S VIEWS ON THE IMPORTANCE OF MULTILEVEL SELECTION BEEN LARGELY IGNORED BY EVOLUTIONARY BIOLOGISTS?

There is little doubt that many animal species, including of course humans, live in groups and that in effect, some groups outcompete others, even destroying rival groups altogether. This is true, for example, in ants and termites in which founding females (and their partners in the case of termites) form small colonies that may succeed in killing or absconding with the members of nearby colonies (eg, Hölldobler and Wilson, 1990; Rissing and Pollock, 1987). Needless to say, similar behavior occurs in human societies that have engaged in genocide and slavery now and in the recent past (and by extension long ago) as some groups and tribes have wiped others out completely (Diamond, 1992).

It is appealing to think that selection can occur at the group level as groups within a species eliminate other groups, thereby affecting the transmission of genes to subsequent generations (to the extent that groups differ genetically). Even Darwin (1859) appeared to have accepted that humans were potentially subject to group selection, although he did not call it that, simply noting that tribes with altruistic members who behaved morally (nicely) toward each other might well outcompete tribes of a less "moral" nature.

And D.S. Wilson has convinced some prominent biologists that he is right about the role of group selection in shaping the social behavior of animals, including humans. Among these recruits is none other than E.O. Wilson (not a relative) who has become a strong advocate of multilevel selection (Wilson and Wilson, 2007, 2008). Even so, the vast majority of human sociobiologists and behavioral ecologists in general have not come around. Why not?

There are several major reasons why group selection theory has not become a driver of research on the social behavior of humans and other animals. The first reason has to do with the history of group selection theory. As D.S. Wilson is fond of noting, most of today's biologists have been influenced directly or indirectly by George C. Williams's book *Adaptation and Natural Selection* in which he explained why group-level explanations for social behavior were almost certainly either wrong or unnecessary. Williams (1966) wrote his book in response to the common view at the time that hypotheses about the group or species benefits of a variety of traits were Darwinian. He showed his readers that they were not.

I was one of those readers who eventually read *Adaptation and Natural Selection* but only after I had as an undergraduate at Amherst College first read V.C. Wynne-Edwards's huge book *Animal Dispersion in Relation to Social Behavior*, a book I found fascinating and wholly persuasive. Wynne-Edwards (1962) began his book with an analysis of the whaling industry in North America. He pointed out that because whalers failed to conserve the resource on which their industry was founded, whalers effectively went extinct having so reduced the populations of right whales, blue whales, and sperm whales among others that there were insufficient numbers of prey to sustain whale hunting. His point was that unless animal species had evolved restraints on their utilization of key resources, they too would have gone extinct. He then proceeded for hundreds of pages to interpret the social interactions of animals as the means by which these species had evolved the necessary social behaviors to keep them from overpopulating the world and driving themselves into extinction. For example, when hordes of starlings gather together and engage in mass flights at certain times of the year, Wynne-Edwards proposed that they were providing one another with the information about the size of the local population of their species so that when the birds reproduced, they could adjust their breeding activities to maintain their numbers at a level consonant with the carrying capacity of the area. Individual birds might lower their clutch size or refrain from breeding altogether if the group was on the verge of getting too large, a decision that would be good for all those dependent on a limited resource. Similarly, Wynne-Edwards noted that in territorial species, individuals that failed to secure a suitable breeding site would sit out the breeding season altogether rather than go on to reproduce. Their failure to breed contributed to the overall production of offspring at an appropriate level, according to Wynne-Edwards, a level that did not constitute a threat to the well-being of the species as a whole.

When I talked to my undergraduate advisor Lincoln Brower about these ideas, which I enthusiastically recounted to him, I was shocked when he told me that he and most other biologists were not similarly persuaded that individuals would sacrifice their reproductive chances to benefit their local population or species. Instead, I learned the essence of Williams's counter-argument from Brower, which in a nutshell was that if there really were individuals that reduced their production of surviving offspring to benefit others, they would in effect be committing genetic suicide. The special alleles that predisposed individuals to behave altruistically for the general good would be quickly lost from the population through the reproductive restraint exhibited by these genetically suicidal altruists.

As my advisor pointed out, the logic of Williams's argument was overwhelming. Instead of positing that such and such a social trait helped the species survive, something that was done often in the mid-20th century and far more casually by persons other than Wynne-Edwards, the logic of Darwinian natural selection theory suggested that biologists would be better served by trying to develop hypotheses about the benefit to the individual and its genes of the trait in question. If starlings really did engage in mass flights that reduced how many eggs individuals laid at a later date, one possible explanation consistent with natural selection is that the birds reduced their reproduction so as not to have most or all of their nestlings die of starvation. By cutting back, the birds might maximize the number of *surviving* offspring they produced, the only ones that could carry their genes into the next generation. Likewise, if nonterritorial birds failed to breed in a given year, one Darwinian hypothesis is that these birds lacked the capacity to acquire a territory with sufficient resources to provide for their offspring. Were they to attempt to breed, their progeny would die without passing on the genes of the parents. But if they were to postpone breeding until they were older and more powerful or until the current territorial individuals had died, freeing up space, the birds that exercised reproductive restraint in one year might go on to have surviving offspring in one or more subsequent years, providing the genetic basis for self-benefiting, temporary reproductive restraint. These hypotheses are testable but for our purposes the point is that these possible explanations do not require that they evolve by a process in which individuals that exhibit restraint and leave fewer surviving offspring (and fewer copies of their genes) than others within their species do so for the good of that species.

Williams not only explained why individual-level hypotheses were consistent with Darwinian theory and why group benefit hypotheses were usually neither Darwinian nor logical, but he provided examples of how to test the alternatives. If, for example, sex ratios had evolved to help species survive over the long haul, then we might expect sex ratios to become heavily female-biased during times when the population had fallen well below the carrying capacity of the environment. But when there were too many individuals to be supported by a region, the sex ratio would be predicted to become male-biased—if sex ratio evolved by Wynne-Edwardsian group selection. These sorts of shifts are not observed in nature providing evidence against a group selection theory of sex ratios. Instead, in the vast majority of species, sex ratios remain consistently at or very near 1:1.

This fact makes adaptive sense if sex ratios are the product of Darwinian natural selection acting on variation among individuals as the following thought experiment makes clear. Imagine a population in which parents happen to produce more daughters than sons, creating a female-biased sex ratio. In this situation, the average reproductive success of a son increases, given the increased opportunities overall that males would have to acquire multiple mates. Thus any genetic variant that predisposes parents for a time to produce more sons than daughters will be favored by natural selection acting at the level of the individual, no matter its effect on the long-term survival of the species. As males become more common in the population as a whole, however, their average reproductive success approaches that of females. If there is an overshoot, leading to a slightly male-biased sex ratio, then selection will shift, favoring parents with a hereditary tendency to produce daughters. When the sex ratio is one to one, however, biasing the production of one sex over the other is not selectively advantageous (since the average reproductive success of both sexes is the same), which is why most sex ratios are in fact 1:1. Thus, sex ratio appears to be a product of natural selection, not Wynne-Edwardsian group selection, an illustration of the point that whereas natural selection theory has produced predictions that are borne out by the evidence, for the good of the species selection theory has not (Williams, 1966). (The exceptions to the rule of a 1:1 sex ratio have also been studied and explained via inclusive fitness theory without resort to group selection thinking (West et al., 2008).)

Williams's book was tremendously influential. Many biologists, myself included, believed that it was the most important book since *On the Origin of Species* because it reminded us of the logical foundations of Darwinian natural selection and led us to be wary of the kind of throwaway hypotheses about group benefits that had become standard by the 1960s. For D.S. Wilson and others interested in reviving group selection, however, the acceptance of Williams's ideas has become so widespread that they have become dogma, preventing most biologists from keeping an open mind about the newer, more sophisticated form of group selection embodied in the term multilevel selection: "Ever since [Williams's book], students have been taught that group selection is possible in principle, but can be ignored in practice" (Wilson and Wilson, 2007). The implication here is that the brainwashing that occurs early in a researcher's career can lead him or her to a lifelong rejection of perfectly plausible ideas.

There is little doubt that *Adaptation and Natural Selection* helped make it difficult for D.S. Wilson to find a receptive audience for his ideas. But not because most evolutionary biologists have become indoctrinated ideologues committed to individual-level selection as a result of their early exposure to and acceptance of the arguments of a key authority. Evolutionary biologists are devoted to Darwin's *On the Origin of Species* and to Williams's *Adaptation and Natural Selection* because of the power of the underlying logic of these books, the abundant supporting evidence that Darwin and Williams presented, and the

utility of these books for the development of productive research programs. As I shall argue, the same cannot be said for multilevel selection theory.

The post—Wynne-Edwardsian group selectionists have been at pains to show that multilevel selection is different from the naïve group selection of the past. The key difference between the old or original form of group selection and the newer forms is that the groups in the newer models are groups *within* species, rather than entire species that are supposed to be striving unconsciously for long-term survival. But in both naïve species-level group selection and the more sophisticated variants proposed by D.S. Wilson and others, individuals give up some chances to reproduce personally to help their group in some way. In Wynne-Edwardsian group selection, the benefit to the group was the management of group size in keeping with the resources available for that species. In Wilsonian multilevel selection, the benefit to the group is the creation of a more cooperative unit capable of more highly coordinated group action. For example, groups with self-sacrificing altruists are said to be able to better deal with other groups with fewer altruists.

As Wilson notes, Williams and others agree that groups sometimes compete with one another in ways that have the potential to alter gene frequencies within the species. But group selection, according to the arguments of Williams and others, is a considerably less potent process for evolutionary change than is reproductive competition among the individual members of a group or species. The best way to imagine this is to envision a scenario in which group selection acts to increase the frequency of an allele that reduces the reproductive success (fitness) of some individuals within that group. Group selection of this sort will be opposed by Darwinian natural selection in favor of competing alleles that do not have the effect of lowering individual fitness. Special conditions are required therefore if the group process is to overwhelm natural selection at the individual level given that altruists will generally fail to reproduce as much as the less altruistic members of the group that benefit from the presence of self-sacrificing individuals. The effects of differences in the survival and reproductive success of groups must exceed that of differences in the inclusive fitness of individuals within groups. This outcome in turn will depend on such things as the degree of genetic differences among versus within groups as well as the generation time of groups versus individuals (Alexander, 1989).

In addition to the point that group selection favors group-level adaptations only when between-group selection is more intense than within-group [natural] selection, West et al. (2008, 2011) argue that group selection theory is further limited in usefulness for researchers for practical reasons. Whereas measurements of relatedness needed for inclusive fitness theory are readily available, calculating the comparable measures needed to establish the fitness of a group is more difficult. The practical difficulties associated with using group selection theory have to be overcome if it is to be used whereas the advocates of inclusive fitness theory can point to a long list of research accomplishments over the past 40 years (West et al., 2008). As a result, when there has been an opportunity to pursue a topic with group selection theory or kin selection theory, researchers have almost universally chosen kin selection theory (West et al., 2008).

Misconception

Natural selection favors selfish, self-centered behavior which means that altruistic, moral, unselfish behavior requires the group selection component of multilevel selection theory for its explanation.

Given that there are good reasons for thinking that multilevel selection theory comes with a number of difficulties associated with its application, those who state that we should use the theory must identify some issues that compel us to become group selectionists to resolve these puzzles. In fact, one of the central issues that supposedly requires multilevel selection theory for its explanation is the occurrence of behavior in group-living animals that is not driven by a me-first selfishness.

Here in an article by D.S. Wilson and Elliott Sober (1994) is a statement that encapsulates this assertion: "an effective group-oriented society cannot be composed of individuals who are motivated solely by a calculus of self-interest. The external social conventions that make free-loading difficult are evidently necessary but not sufficient and must be supplemented by a psychological attitude of genuine concern for others; a direct calculus of group interest rather than self interest is essential."

The idea that natural selection will inevitably result in the evolution of individuals who are *motivated* to behave selfishly (in the everyday meaning of the word) is repeated in the blurb on Amazon.com for the book *Unto Others* by Sober and Wilson (1998): "No matter what we do, however kind or generous our deeds may seem, a hidden motive of selfishness lurks—or so science has claimed for years. This book, whose publication promises to be a major scientific event, tells us differently. In *Unto Others* philosopher Elliott Sober and biologist David Sloan Wilson demonstrate once and for all that unselfish behavior is in fact an important feature of both biological and human nature."

Or, as the group selectionist convert E.O. Wilson puts it in his op-ed piece for the *New York Times*, "risking oversimplification, individual selection promoted sin, while group selection promoted virtue" (http://opinionator.blogs.nytimes.com/2012/06/24/evolution-and-our-inner-conflict/).

It is difficult for me to believe that the leading thinkers on multilevel selection can have confused the immediate

(ie, motivational) causes of our behavior with the ultimate (evolutionary) causes, but they have. As these quotes make clear, we are asked to believe that, according to Williams and others, if we are to succeed in passing on our genes, we have to *want* to boost our genetic success. No one, however, thinks that because men want to copulate with relatively young women that they do so because they hope to leave more copies of their genes than men who are motivated to copulate only with older women. Our proximate psychological mechanisms can get us to do what is in the interests of our genes without providing us with an awareness of the ultimate significance of our desires and actions (Alcock, 2013; Gaulin and McBurney, 2001).

Just as critics of Richards Dawkins's book *The Selfish Gene* (1976) failed to grasp the meaning of a metaphor, so too multilevel proponents would have us take the words "selfish" and "altruistic" literally, ie, as in everyday English when these words do imply something about the intentions of the actor. But in reality, evolutionary biologists use the word "selfish" only to mean "reproductively successful" or "genetically successful," and "altruism" in this lexicon only means "self-sacrificing in reproductive terms." Thus it is entirely possible for an altruistic act to be "selfish" in the evolutionary sense of advancing an individual's genetic contribution to the next generation. As noted earlier, altruism is adaptive (selected for) when the cost to the individual in terms of personal reproduction (or direct fitness) is outweighed by the gain to the individual in terms of the increase in a relative's reproductive success times the degree of relatedness between the altruist and the relative (or indirect fitness). This is Hamilton's rule, and a very useful rule it is in evolutionary biology.

Thus, natural selection and kin selection acting at the level of the individual favor whatever behavioral tendencies, intentions, motivations and the like advance the actor's genetic success, regardless of whether the actor is aware of the evolved function of his, her, or its desires, wishes, or intentions. If by behaving nicely to others, ie, being moral, an individual gains a reputation for being a nice person, and thereby increases his or her chances of producing surviving offspring, then the behavior is "selfish" in evolutionary terms. If by helping relatives, an individual increases his or her indirect fitness so much that it more than compensates for any loss of direct fitness, then the altruism of the individual is "selfish," again in evolutionary terms. Group selection theory is not needed to explain why "unselfish" (in Wilsonian terms) behavior has evolved in so many organisms.

Misconception

Kin selection theory alone cannot account for the evolution of many kinds of cooperative behavior within groups.

Once we get past the semantic issues and the confusion engendered by mixing everyday and evolutionary meanings of the words "selfish" and "altruistic," we can begin to evaluate competing claims about the role of kin selection versus group selection in the evolution of social behavior, especially cooperative social actions. Remember that kin selection can favor the kind of self-sacrificing behavior that helps relatives reproduce more than they would have otherwise. Multilevel selectionists appear to have realized the danger that Hamiltonian kin selection poses to their arguments because as noted earlier they would have us believe that altruism of any sort (such as that expressed when humans behave morally with respect to their relatives) requires group selection for its evolution. One way in which to strengthen the case for this position is to call kin selection outmoded, overblown, or just plain wrong.

Perhaps the most notable example of this approach comes from a research report by Nowak et al. (2010). This paper was written with E.O. Wilson as a coauthor, who by then had renounced positions taken in *Sociobiology* (1975). E.O. Wilson now claims that group selection has played a major role in the evolution of the sterile (ie, altruistic) castes present in colonies of certain insects (Wilson and Hölldobler, 2005). In support of this position, Nowak and his colleagues dismissed kin selection theory via a mathematical model as well as by identifying its supposed failures on evidentiary and practical grounds. For example, they said that kin selection had failed because it is now recognized that the unusual sex determination system of the Hymenoptera (bees, ants, and wasps) almost certainly has *not* played a central role in the evolution of sterile castes of the social bees, ants, and wasps. In contrast, Hamilton (1964) had once proposed that the fact that male Hymenoptera were haploid and females were diploid could have contributed to the abundance of highly social species in this order of insects. As Hamilton explained, if a female bee, ant, or wasp mates with just one male, her daughters will all share the same genes that are present in the genetically identical sperm of the haploid male, a factor that results in an unusually high level of genetic relatedness among those daughters. The boost in relatedness should, all other things being equal, make it more likely for females to gain fitness indirectly by helping certain of their sisters to reproduce, resulting eventually in the evolution of a sterile or near-sterile female worker caste in the social Hymenoptera. As mentioned, these insects do feature a female worker caste that rarely attempts to reproduce but instead helps in the production of potentially reproducing members of the next generation.

Although female workers are indeed the rule in the social Hymenoptera, it is now known that in many species the queens that found new colonies mate with several males, which greatly reduces the genetic similarity of their daughters and might, if haplodiploidy were the only factor

affecting the indirect fitness of sisters that help other sisters, reduce the indirect fitness of altruistic (ie, worker) individuals. Despite the lowered genetic relatedness of the workers, however, these females continue to sacrifice on behalf of others in their colony. Moreover, as Hamilton himself noted, there are highly social insects that lack the special sex determination mechanisms of the bees, ants, and wasps, most notably the termites, in which both males and females are diploid and yet these insects are every bit as highly social as the social bees, ants, and wasps. Because haplodiploidy is not essential for the evolution of a sterile worker caste, we must, according to Nowak et al. (2010), conclude that kin selection is not a driver of altruism in the social insects. In addition, Nowak and his colleagues went on to assert that kin selection theory had proven of little use for behavioral biologists. In other words, not only was it possible to demonstrate mathematically that kin selection could be ignored, but there was field evidence against the theory as well as practical reasons for dismissing the idea.

The paper by Nowak et al. (2010) generated a strong response from adaptationists who have accepted kin selection and inclusive fitness theory as important amendments to Darwinian natural selection. Adaptationists, most of them behavioral ecologists, provided a collective rebuttal (Abbot et al., 2011) that made two major points: first, the haplodiploid basis for the evolution of a sterile worker caste is not central to kin selection theory (see also http://old.richarddawkins.net/articles/508102-a-misguided-attack-on-kin-selection) and second, the theory has, contra Nowak et al. (2010), been responsible for all manner of research discoveries about the evolution of cooperative behavior (a point that has been long documented; see Queller and Strassman, 1998; Strassmann and Queller, 2007).

A key argument presented by Abbot et al. (2011) is that haplodiploid sex determination is not central to the theory of kin selection as applied to the evolution of altruism. All that is required (as noted previously) is that the cost to an individual in lost personal reproduction be exceeded by the increase in another individual multiplied by the degree of relatedness between the helper and the helpee. The fitness cost of help and its reproductive effect on another have often been ignored thanks to all the attention given to *r*, the coefficient of relatedness between the altruist and the individual it helps (Herbers, 2006). A high degree of relatedness can move the needle toward altruism but so can a low cost for the helper and so can a large benefit for the helpee. Haplodiploidy is only one of many factors that can potentially affect the genetic gains or losses from helping relatives. Assorted ecological factors can also strongly affect the costs of helping as well as the benefits to individuals that receive this help (Andersson, 1984).

In addition, the utility of kin selection theory has been established beyond a doubt in a great many arenas, contrary to the claims of Nowak et al. (2010). Kin selection theory has led to powerful explanations of many forms of cooperation and altruism, alarm calling, the allocation of resources from parents to offspring of the two sexes, policing by colony members and rejection of nonkin from colonies, conflict within generally cooperative units, and so on (Abbot et al., 2011). Note especially that conflict *does* occur within groups of social animals and when it does happen, kin selection theory has provided solutions, often by showing researchers that the individuals in opposition are genetically dissimilar (Queller and Strassmann, 1998).

In contrast, the practical utility of the group selection component of multilevel selection has been disputed (West et al., 2011). For one thing, different authors have proposed several different forms of the "new" group selection in addition to the group selection component of multilevel selection (West et al., 2011). This fact leads to confusion when trying to test hypotheses that a social animal possesses group-level adaptations that are the result of group-level processes. In addition, most of the work on group selection theory has taken place via the development of models designed to demonstrate the feasibility of the process and in laboratory experiments designed to show that under certain carefully controlled conditions, group selection can indeed occur (Wade, 1976, 1978). These experiments typically involve groups that are designed to be as much like families as possible with maximum genetic differences among groups and short generation times (Alexander, 1989). Indeed, the assumptions of these models, especially those having to do with population structure, play an important role in whether one concludes that it is even possible for group selection to occur (Molleman et al., 2013). Very few applications of the theory have been done under natural conditions with "real" organisms with the intent to test predictions derived from the theory on the assumption that the trait(s) under investigation promote the welfare or success of groups over the inclusive fitness of individuals.

Misconception

Only group selection theory can account for cooperation among unrelated individuals that live in social groups.

But if altruism can often be explained by kin selection, what about the evolution of cooperation in groups composed of unrelated individuals? The fact that these individuals do not share alleles in common by shared descent means that the kin (or indirect) component of selection cannot be responsible for the evolution of the helpful behavior seen in such groups. Therefore, some group selectionists have concluded, cooperative behavior must have evolved via selection at the level of the group of unrelated individuals, an argument that has been applied to the colonies of social insects that are composed of both kin and nonkin. Often unrelated individuals in these colonies

cooperate to the same extent that related colony members do (Korb and Heinz, 2004), which has led some to argue that their behavior is the product of group selection for the resolution of conflict within the greater group.

The claim that group selection is needed to explain cooperation among unrelated individuals living in groups is odd given that in numerous cases, members of different species, which are obviously not related to one another, work together in ways that clearly benefit all the individuals of the different species. Consider the occurrence of mixed-species flocks of birds, in which the members of one species respond to the alarm signals given by others with the entire flock then fleeing from an approaching predator. The alarm givers might benefit by getting others to join with them in forming a large, difficult-to-attack mass of birds in flight; the joiners might gain by reducing the risk that they will be left behind where they will be vulnerable to an attacking predator. There are several other mutualistic hypotheses that have been tested via observation of mixed-species associations (eg, Campobello et al., 2012; Goodale et al., 2010). The point is that being part of a group of unrelated individuals does not eliminate the possibility that group-related behaviors provide a survival (reproductive) benefit for all concerned—even if they are members of different species and therefore unrelated to one another.

The same applies to groups composed entirely of the members of a single species, some of which are unrelated to others (Krams et al., 2010; Sherman, 1985). It is well established, for example, that male lions form coalitions that may or may not be made up of relatives such as brothers or cousins (Grinnell et al., 1995; Packer and Pusey, 1982). A coalition made up of unrelated males may nevertheless be able to overwhelm a single male (or a smaller coalition) that has monopolized the sexual services of the female members of a pride. Were each unrelated male to tackle an established pride master by himself, the newcomer singletons would almost certainly fare less well than unrelated males that work together when competing for control of a pride. Should a coalition of unrelated males take a pride from others, all the members of the successful coalition have some chance of reproducing (albeit not necessarily the same chance) in part because females often come into estrous simultaneously (Packer and Pusey, 1982). The logic of natural selection theory suggests that some chance of reproducing is better (for the cooperator's genes) than no chance of reproducing. Thus, cooperation among nonrelatives can spread through a species via natural selection acting on individuals without the need to invoke group selection.

We can use this approach when reevaluating one of the putative examples of group selection—shaping animal behavior (see Dugatkin, 2002), a case involving a leafcutter ant, *Acromyrmex versicolor*, that forms small groups of unrelated foundress females after the winged forms have been released from their colonies. These females live in the same underground burrow and cooperate in the sense of attacking other groups together while defending themselves from assaults by other mini-colonies nearby. They do not form dominance hierarchies so that the individuals that take on the risky task of gathering food from the desert for the group are not different in body size on average from the others in an incipient colony. In other words, the cooperative foragers are not contributing to the reproductive success of relatives nor are they making the best of a bad job, having been forced by their more dominant companions to do the dangerous job of foraging. The explanation for this behavior favored by group selectionists is that although cheating would be favored by natural (individual-level) selection, the survival of any member of the group depends on the ability of the group to find enough food and to fend off aggressive groups around them. The aggressive competition between groups is said to generate a form of group selection.

But the tolerance of individuals of unrelated cooperators and their readiness to forage despite the mortality costs of the behavior could just as easily be said to arise from natural selection acting in a setting in which the odds that an individual will be a surviving queen with a flourishing colony of her own is utterly dependent on the ability of individuals to make it through the early colony establishment phase (Bernasconi and Strassmann, 1999). In this period, females that refuse to accept unrelated foundress queens in their nest or try to "cheat" by letting others do the risky job of foraging are very likely to die quickly when their nests are overwhelmed by rival raiders or when their group is weakened by a shortage of food that makes them vulnerable to attack from others (Strassmann, 1989). In the ant species, *Veromessor pergandei*, which behaves similarly to *A. versicolor*, starting colonies with multiple foundresses have greater success in brood raiding than those with single queens (Rissing and Pollock, 1987).

In other words, many (most?) cases in which unrelated individuals help one another are examples of a naturally selected *mutualism*, with the direct benefits of helping (an increase in the odds of surviving to reproduce) outweighing the fitness costs of cooperating. At the very least, group selectionist hypotheses must be matched against hypotheses based on mutual benefit cooperation with a demonstration that the predictions from the two kinds of hypotheses are not the same, if we wish to discriminate between the two kinds of hypotheses.

WHAT ABOUT HUMANS?

Humans are a highly social species with a great capacity for cooperation. Wilson believes that group selection theory will prove to be especially useful for an understanding of our own behavior. Indeed, the application of group

selection theory to human behavior has a long history if, as noted earlier, we accept that Darwin (1859) considered the idea in *On the Origin of Species* and suggested that moral behavior might help members of one group defeat members of another in a competition between tribes. However, as Ruse (1980) points out, Darwin devoted only a few paragraphs to the possibility of group selection in a book that was overwhelmingly devoted to an explanation of how natural selection might work at the individual level. Thus, any appeal to Darwin as an authority on the subject of group selection is weak at best.

Nonetheless, the desire to believe that we are a special species, with a particularly strong capacity for generosity and moral behavior, expresses itself in many ways. For example, Francis Collins (a leading scientist and current director of the National Institutes of Health), and doubtless many others, feel that the moral behavior of humans is fundamentally religious in nature and cannot be explained in evolutionary terms (Collins, 2007). Although few scientists agree with Collins that God was involved in making us a moral creature, some are convinced that the cooperative nature of humans really is exceptional. Experiments that explore this aspect of our behavior include those in which a person is given only a single chance to secure a financial reward in an experimental game with another individual with whom they will not interact again. The economically rational response would be for the main "player" to take all the money he or she is offered but instead many people give a portion of the proceeds they might otherwise reap to the other player (eg, Fehr and Fishbacher, 2003; Gintis et al., 2003; but see Burton-Chellew and West, 2013). Sharing is not encouraged or required but even so many of those participating in experiments of this sort do share the money they receive.

One explanation for this apparent eagerness to cooperate altruistically is that humans exhibit "strong reciprocity," namely the strong tendency to help others (and to punish those that fail to cooperate). Wilson (2007) considers researchers studying strong reciprocity to be in his camp inasmuch as strong reciprocity could be the basis for the maintenance of cohesive groups. But as West et al. (2011) point out, the strong reciprocity explanation is not evolutionary but instead focuses on the properties of underlying psychological mechanisms that motivate us to do some things rather than others. Proximate explanations of this sort leave unanswered the question of *why* selection (broadly defined) has resulted in the spread of the psychological attributes that induce individuals to do certain things, not others.

For multilevel selectionists, the great cooperative potential of people might be explained in evolutionary terms as a result of selection for group-level adaptations given that the cooperative propensity of humans often leads us to form groups that compete effectively with other groups. But before we go further down this road, let us consider whether we really are as unique as is so often claimed. Certainly we are not more altruistic than sterile worker ants or wasps. Moreover, as noted already, many other species exist in which unrelated individuals work together for mutual gain while also punishing noncooperators in the group (West et al., 2011). It seems probable that we tend to overrate the specialness of *Homo sapiens*.

True, humans seem to engage in far more reciprocal cooperation than most other animals (West et al., 2011). In behavior of this sort, the helper is more than repaid at a later date for his or her cooperative behavior, either by the individual that he or she helped or by relatives of the helpee. Reciprocal cooperation (as distinct from strong reciprocity) has obvious potential fitness benefits for all participants and does not rely on group selection theory for its explanation.

Throughout discussions about the level of selection, proponents of multilevel selection seem to be arguing that living in groups almost automatically leads to group selection. Now no one disagrees with the claim that humans have lived in small societies for much of our evolutionary history nor is there any doubt that groups have interacted aggressively with one another frequently during this time (Bowles, 2009). But group living does not guarantee that evolution will lead to adaptations that help entire groups survive or reproduce at cost to some individuals within these groups. Alexander (1979, 1987) has written extensively on attributes that help bands of people in competition with others but he has been able to use inclusive fitness theory to explain why such things as group-centered morality could have spread through our species. For adaptationists, human ideas about what is moral have almost certainly spread because they led our ancestors to help their kin, thereby raising the helpers' indirect fitness, or because they promoted the kind of group cohesiveness that raised our ancestors' direct fitness during conflicts arising between groups. Cooperation among nonrelatives, including reciprocal assistance, might be especially beneficial for members of our species when defending resources against other aggressive bands nearby or when attempting to take resources from neighboring tribes. Even the heroic self-sacrifice of warriors who die in combat can be explained in terms of the indirect reputational benefits that the deceased fighter confers on his kin, benefits that could translate into increased fitness for the relatives that the dead man left behind (Alexander, 1989). Alexander not only has seen no need to invoke group selection to explain such things as our selective morality, he has actively argued against the utility of the theory of group selection as applied to our species (Alexander, 1989). Again, given that there are alternative hypotheses for such things as tribal affiliation and cooperation within groups, should not multilevel selectionists explicitly contrast their explanations with alternative hypotheses, showing exactly why group

selection theory is required and why the predictions from this theory are more often met than predictions from inclusive fitness theory?

Cultural Group Selection

One other group selectionist argument as applied to human behavior deserves our attention because we are unquestionably special in the extent to which cultural traditions shape our behavior. Proponents of cultural group selection argue that the success of a group depends on the cultural traditions that the society possesses (eg, Boyd and Richerson, 2005, 2010). As a result, over time, some groups (and their special cultures) replace others in a kind of group selectionist process based on cultural traits rather than genetic ones.

Before analyzing cultural group selection theory, we must first deal with the temptation to conclude that sociocultural hypotheses about human behavior should take precedence over "biological" explanations for our social nature. However, sociocultural hypotheses provide immediate or proximate explanations for why we behave the way we do without explaining why in evolutionary terms we possess the proximate mechanisms that enable us to be a sociocultural animal (Alcock and Crawford, 2008). Moreover, just because human behavior is learned and culturally shaped does not mean that our actions are "environmental," free from the effects of standard evolutionary processes based on differences in the inclusive fitness of group members. In reality, all behavioral traits, including learned ones, are the developmental product of an interaction between the organisms' genes and its environment.

The clearest demonstrations of this point come from studies of song learning in birds and language acquisition in humans. Both traits depend on the structure and functional design of the nervous systems that underlie song learning and language acquisition (Alcock, 2013). The white-crowned sparrow that learns its species' territorial song does so because of a complex of brain systems that could not have developed without genetic involvement. Humans who learn Urdu or English do so because of a complex of brain systems whose development depended on the genes in young brain cells. The fact that the white-crowned sparrow male attends to and learns its song by listening to members of its own species while ignoring the songs of other species tells us that the bird's brain mechanisms have evolved to bias learning in ways that promote individual reproductive success. The same is true of our own species with an infant's brain predisposed to detect word sounds from the mass of acoustical information that he or she receives, an ability that contributes to language acquisition by the baby (eg, Saffran, 2001). Cultural traditions are certainly interesting and deserving of explanation. For natural selectionists, cultural learning and the differences among groups that result from our traditions reflect the ability of the human brain to adopt a range of behavioral options, but not an infinite range, with instead biases and peculiarities that induce us to behave in ways that are usually adaptive in the kinds of environments our ancestors experienced or were adaptive during the period when the brain was evolving by standard Darwinian processes. This is a testable proposition and has indeed been repeatedly tested by sociobiologists (broadly defined) and by evolutionary psychologists (eg, Barkow et al., 1992; Pinker, 2002).

Thus, even though we are obviously a highly cultural animal, it is reasonable to ask whether the ability to acquire cultures evolved and if so, by what process—cultural group selection acting on differences *between* groups or standard natural selection acting on differences *within* groups in the inclusive fitness of individuals? Note that learned cultural traditions can lead kin to help kin or they can provide mutual reproductive benefits for all those within a group, whether related or not. Consider religious beliefs, which vary greatly from culture to culture, are universal and highly important in the social behavior of humans.

Religion and Human Behavior

Wilson (2002) has written about religion in the context of cultural group selection. For him and other adherents of this theory, religions are functional in the sense of being a cultural adaptation that encourages individuals to sacrifice for the well-being of their group, sometimes to compete more effectively with other groups, sometimes not. Whatever the case, religious belief contributes to selection at the group level according to Wilson. But it is not as if this is the only explanation for religious traditions, even though Wilson (2002) does not acknowledge or explore individual-level alternatives in his book on the subject (Sosis, 2003). There, Wilson makes much of the fact that the Nuer defeated the Dinka supposedly as a result of their superior social organization (presumably affected by their religious beliefs) as outlined in *The Nuer Conquest* (Kelly, 1985).

But it is not enough to show that people live in groups that sometimes compete aggressively with other groups, each with their own religious beliefs, to demonstrate that cultural group selection is responsible for the religiously sanctioned sacrifices made by some within a tribe or society. For one thing, all the members of a group that prevails over another enjoy the inclusive fitness benefits of success of this sort. Relatives within the winning group may derive indirect fitness gains; nonrelatives may share the spoils of victory in a mutually beneficial manner leading to gains in personal reproduction. In other words, the simple fact that in our species culturally different groups sometimes

compete is *not* evidence in itself of group-level cultural selection.

Moreover in his one attempt to test his multilevel selection hypotheses, Wilson (2005) fails to set his favored approach against any alternative. For him, it is enough that in a random sample of 35 religions, most seem to be designed to deal with economic or other functional issues while encouraging or enforcing behavior that strengthens the bonds that hold religious entities together. Wilson notes that some selection at the individual level is likely to occur in the evolution of religious beliefs but he does not specify what the individual-level effects might be nor how one would evaluate the relative strength of individual-level versus group-level selection during the evolution of religious beliefs. Because he never clearly sets predictions from a group selectionist model against those arising from various adaptationist hypotheses, the picture that he paints remains muddled.

Alexander (1982) sees the conflicts that are inherent in religious societies (and these are acknowledged by Wilson (2002)) as the product of selection in favor of individuals capable of both self-promoting and group-promoting behavior because both kinds of behavior can, under some circumstances, advance the fitness of individuals. For example, Sosis and Bulbulia (2011) treat the costly activities associated with many religious rituals as a way in which individuals can signal their commitment to their co-religionists, the better to secure their cooperation in activities that confer benefits on all concerned. If true, religious ceremonies and other cultural trappings of various sorts are the foundation for mutualisms (Sosis and Alcorta, 2003).

CONCLUSION

Because of the possibilities for confusion when using group selection theories, because of the practical advantages of an individual-level approach, and because of a long history of utility of inclusive fitness theory for researchers in testing predictions derived from individual-level selection, the group selection component of multilevel selection theory has proven no more attractive for most researchers dealing with human behavior than it has for behavioral ecologists and sociobiologists studying the social behavior of other vertebrates. In one review of human behavioral ecology, group selection is not even mentioned (Nettle et al., 2013). Instead, the authors claim that "central to [human behavioral ecology] is the adaptationist stance," an approach based on inclusive fitness theory.

If someone wishes to test modern group selectionist hypotheses, then more power to that person. These individuals should, however, specify exactly what trait they are interested in explaining before identifying the form of group selection theory they are using. Then, after demonstrating that it is feasible to measure among-group genetic variation accurately, they will need to "determine the fitness consequences of phenotypic variation within and among groups" (Sober and Wilson, 1998). This is an onerous requirement but necessary to show that selection among groups is either more powerful than selection against certain behavioral traits within groups or at the very least that selection at the group level reinforces natural selection among individuals. To date, these criteria have not yet been achieved in research with nonhuman animals living under natural conditions nor have they been secured in studies of humans. For most human sociobiologists, the adaptationist stance based on inclusive fitness theory will continue to be the approach of choice.

ACKNOWLEDGMENTS

I am indebted to Stuart West and his colleagues for their clear and convincing papers on the evolutionary study of cooperation. Ron Rutowski read a draft of my chapter and made many helpful suggestions for its improvement.

REFERENCES

Abbot, P., Abe, J., Alcock, J., et al., 2011. Inclusive fitness theory and sociality. Science 471, E1–E4.

Alcock, J., 2001. The Triumph of Sociobiology. Oxford University Press, New York.

Alcock, J., 2013. Animal Behavior: An Evolutionary Approach, tenth ed. Sinauer Associates, Sunderland, MA.

Alcock, J., Crawford, C., 2008. Evolutionary questions for evolutionary psychologists. In: Crawford, C., Krebs, D.L. (Eds.), Foundations of Evolutionary Psychology. Lawrence Erlbaum Associates, New York.

Alexander, R.D., 1979. Darwinism and Human Affairs. University of Washington Press, Seattle, WA.

Alexander, R.D., 1987. The Biology of Human Morality. Aldine de Gruyter, Hawthorne, NY.

Alexander, R.D., 1982. Biology and the moral paradoxes. Journal of Biological Structures 5, 389–395.

Alexander, R.D., 1989. Evolution of the human psyche. In: Mellars, P., Stringer, C. (Eds.), The Human Revolution: Behavioral and Biological Perspectives on the Origins of Modern Humans. Princeton University Press, Princeton NJ.

Allen, E., et al., November 13, 1975. Against "sociobiology". The New York Review of Books 22.

Andersson, M., 1984. The evolution of eusociality. Annual Review of Ecology and Systematics 15, 165–189.

Barkow, J.H., Cosmides, L., Tooby, J. (Eds.), 1992. The Adapted Mind: Evolutionary Psychology and the Generation of Culture. Oxford University Press, New York.

Bernasconi, G., Strassmann, J., 1999. Cooperation among unrelated individuals: the ant foundress case. Trends in Ecology and Evolution 14, 477–482.

Bowles, S., 2009. Did warfare among ancestral hunter-gatherers affect the evolution of human social behaviors? Science 324, 1293–1298.

Boyd, R., Richerson, P.J., 2005. The Origin and Evolution of Cultures. Oxford University Press, Oxford.

Boyd, R., Richerson, P.J., 2010. Transmission coupling mechanisms: cultural group selection. Philosophical Transactions of the Royal Society (B) 365, 3787–3795.

Buller, D.J., 2005. Adapting Minds: Evolutionary Psychology and the Persistent Quest for Human Nature. MIT Press, Cambridge, MA.

Burton-Chellew, M.N., West, S.A., 2013. Prosocial preferences do not explain human cooperation in public-goods games. Proceedings of the National Academy of Sciences of the United States of America 110, 216–221.

Buss, D.M., 1989. Sex differences in human mating preferences: evolutionary hypotheses tested in 37 cultures. Behavioral and Brain Sciences 12, 1–49.

Buss, D.M., 2013. The science of human mating strategies: an historical perspective. Psychological Inquiry 24, 171–177.

Buss, D.M., Haselton, M., 2005. The evolution of jealousy: a reply to Buller. Trends in Cognitive Sciences 9, 506–507.

Buss, D.M., Schmidt, D.P., 1993. Sexual strategies theory: an evolutionary perspective on human mating. Psychological Review 100, 204–232.

Campobello, D., Sara, M., Hare, J.F., 2012. Under my wing: lesser kestrels and jackdaws derive reciprocal benefits in mixed-species colonies. Behavioral Ecology 23, 425–433.

Collins, F.S., 2007. The Language of God: A Scientist Presents Evidence for Belief. Free Press, New York.

Confer, J.C., Easton, J.A., Fleischman, D.S., Goetz, C.D., Lewis, D.M.G., Perilloux, C., Buss, D.M., 2010. Evolutionary psychology: controversies, questions, prospects and limitations. American Psychologist 65, 110–126.

Daly, M., Wilson, M., 1999. Human evolutionary psychology and animal behaviour. Animal Behaviour 57, 509–517.

Darwin, C., 1859. On the Origin of Species. Murray and Sons, London.

Dawkins, R., 1976. The Selfish Gene. Oxford University Press, New York.

Diamond, J., 1992. The Third Chimpanzee. HarperCollins, New York.

Dugatkin, L.A., 2002. Animal cooperation among unrelated individuals. Naturwissenschaften 89, 533–541.

Dunbar, R.I.M., Barrett, L., 2007. Evolutionary psychology in the round. In: Dunbar, R.I.M., Barrett, L. (Eds.), The Oxford Handbook of Evolutionary Psychology. Oxford University Press, London.

Ehrlich, P., 2000. Human Natures: Genes, Cultures, and the Human Prospect. Island Press, Washington, D.C.

Fehr, E., Fischbacher, U., 2003. The nature of human altruism. Nature 425, 785–791.

Gannon, L., 2002. A critique of evolutionary psychology. Psychology Evolution and Gender 4, 173–218.

Gardner, A., West, S.A., Wild, G., 2011. The genetical theory of kin selection. Journal of Evolutionary Biology 24, 1020–1043.

Gaulin, S.J.C., McBurney, D.H., 2001. Psychology: An Evolutionary Approach. Prentice Hall, Upper Saddle River, NJ.

Gintis, H., Bowles, S., Boyd, R., Fehr, E., 2003. Explaining altruistic behavior in humans. Evolution and Human Behavior 24, 153–172.

Goodale, E., Beauchamp, G., Magrath, R.D., Nieh, J.C., Ruxton, G.D., 2010. Interspecific information transfer influences animal community structure. Trends in Ecology and Evolution 25, 354–361.

Gould, S.J., Lewontin, R., 1979. The spandrels of San Marco and the Panglossian paradigm: a critique of adaptationist thought. Proceedings of the Royal Society of London B 205, 581–598.

Grinnell, J., Packer, C., Pusey, A.E., 1995. Cooperation among male lions: kinship, reciprocity or mutualism? Animal Behaviour 49, 95–105.

Herbers, J.M., 2006. Darwin's one special difficulty: celebrating Darwin 200. Biology Letters 5, 214–217.

Hamilton, W.D., 1964. The genetical evolution of social behavior, I and II. Journal of Theoretical Biology 7, 1–52.

Hagen, E., 2005. Controversial issues in evolutionary psychology. In: Buss, D.M. (Ed.), The Handbook of Evolutionary Psychology. Wiley, Hoboken, New Jersey.

Hölldobler, B., Wilson, E.O., 1990. The Ants. Belknap Press, Cambridge, MA.

Kelly, R.C., 1985. The Nuer Conquest: The Structure and Consequences of an Expansionist System. University of Michigan Press, Ann Arbor, MI.

Kenrick, D.T., 1995. Evolutionary theory and the confederacy of dunces. Psychological Inquiry 6, 56–61.

Kenrick, D.T., 2011. Sex, Murder and the Meaning of Life. Basic Books, New York.

Korb, J., Heinze, J., 2004. Multilevel selection and social evolution of insect societies. Naturwissenschaften 91, 291–304.

Krams, I., Berzins, A., Krama, T., Wheatcroft, D., Igaune, K., Rantala, M.J., 2010. Increased risk of predation increases cooperation. Proceedings of the Royal Society of London B 277, 513–518.

Lopreato, J., Crippen, T., 1999. Crisis in Sociology: The Need for Darwin. Transaction Publishers, New Brunswick, NJ.

Menken, J., Trussell, J., Larsen, U., 1986. Age and infertility. Science 233, 1389–1394.

Molleman, L., Quinones, A.E., Weissing, F.J., 2013. Cultural evolution of cooperation: the interplay between forms of social learning and group selection. Evolution and Human Behavior 34, 342–349.

Nettle, D., Gibson, M.A., Lawson, D.W., Sear, R., 2013. Human behavioral ecology: current research and future prospects. Behavioral Ecology 24, 1031–1040.

Nowak, M.A., Tarnita, C.E., Wilson, E.O., 2010. The evolution of eusociality. Nature 466, 1057–1062.

Packer, C., Pusey, A.E., 1982. Cooperation and competition within coalitions of male lions: kinship or game theory. Nature 296, 740–742.

Pinker, S.A., 2002. The Blank Slate: The Denial of Human Nature. Viking Press, New York.

Queller, D.C., Strassmann, J.E., 1998. Kin selection and social insects. Bioscience 48, 165–175.

Reeve, H.K., 2000. Unto others: the evolution and psychology of unselfish behavior. Evolution and Human Behavior 21, 65–72.

Rissing, S.W., Pollock, G.B., 1987. Queen aggression, pleometrotic advantage, and brood raiding in the ant *Veromessor pergandei* (Hymenoptera: Formicidae). Animal Behaviour 35, 975–981.

Rose, H., Rose, S. (Eds.), 2000. Alas, Poor Darwin: Arguments against Evolutionary Psychology. Jonathan Cape, London.

Ruse, M., 1980. Charles Darwin and group selection. Annals of Science 37, 615–630.

Saffran, J.R., 2001. Words in a sea of sounds: the output of infant statistical learning. Cognition 81, 149–169.

Sherman, P.W., 1985. Alarm calls of Belding's ground squirrels to aerial predators: nepotism or self-preservation? Behavioral Ecology and Sociobiology 17, 313–323.

Smith, E.A., Borgerhoff Mulder, M., Hill, K., 2001. Controversies in the evolutionary social sciences. Trends in Ecology and Evolution 16, 128–135.

Sober, E., Wilson, D.S., 1998. Unto Others: The Evolution and Psychology of Unselfish Behavior. Harvard University Press, Cambridge, MA.

Sosis, R., 2003. Review of Darwin's Cathedral: evolution, religion and the nature of society by David Sloan Wilson. Evolution and Human Behavior 24, 137–143.

Sosis, R., Alcorta, C.S., 2003. Signaling, solidarity and the sacred: the evolution of religious behavior. Evolutionary Anthropology 12, 264–274.

Sosis, R., Bulbulia, J., 2011. The behavioral ecology of religion: the benefits and costs of one evolutionary approach. Religion 41, 341–362.

Strassmann, J.E., 1989. Altruism and relatedness at colony foundation in social insects. Trends in Ecology and Evolution 4, 371–374.

Strassmann, J.E., Queller, D.C., 2007. Insect societies as divided organisms: the complexities of purpose and cross-purpose. Proceedings of the National Academy of Sciences of the United States of America 104, 8619–8626.

Wade, M.J., 1976. Group selection among laboratory populations of Tribolium. Proceedings of the National Academy of Sciences of the United States of America 173, 4604–4607.

Wade, M.J., 1978. A critical review of the models of group selection. Quarterly Review of Biology 53, 101–114.

Webster, G.D., 2007. Evolutionary psychology's increasing role in personality and social psychology. Evolutionary Psychology 5, 84–91.

West, S.A., Griffin, A.S., Gardner, A., 2008. Social semantics: how useful has group selection been? Journal of Evolutionary Biology 21, 374–385.

West, S.A., El Mouden, C., Gardner, A., 2011. Sixteen common misconceptions about the evolution of cooperation in humans. Evolution and Human Behavior 32, 231–262.

Williams, G.C., 1966. Adaptation and Natural Selection. Princeton University Press, Princeton, NJ.

Wilson, D.S., 1975. A theory of group selection. Proceedings of the National Academy of Sciences of the United States of America 72, 143–146.

Wilson, D.S., 2002. Darwin's Cathedral: Evolution, Religion and the Nature of Society. University of Chicago Press, Chicago, IL.

Wilson, D.S., 2005. Testing major evolutionary hypotheses about religion with a random sample. Human Nature 16, 419–446.

Wilson, D.S., 2007. Group level evolutionary processes. In: Dunbar, R.I.M., Barrett, L. (Eds.), Handbook of Evolutionary Psychology. Oxford University Press, New York.

Wilson, D.S., Sober, E., 1994. Reintroducing group selection to the human behavioral sciences. Behavioral and Brain Sciences 17, 585–684.

Wilson, D.S., Wilson, E.O., 2007. Rethinking the theoretical foundation of sociobiology. Quarterly Review of Biology 82, 327–348.

Wilson, D.S., Wilson, E.O., 2008. Evolution for "the good of the group." American Scientist 96, 380–389.

Wilson, E.O., 1975. Sociobiology: The New Synthesis. Harvard University Press, Cambridge, MA.

Wilson, E.O., 1994. Naturalist. Island Press, Washington, D.C.

Wilson, E.O., Hölldobler, B., 2005. Eusociality: origins and consequences. Proceedings of the National Academy of Sciences of the United States of America 102, 13367–13371.

Wynne-Edwards, V.C., 1962. Animal Dispersion in Relation to Social Behaviour. Oliver and Boyd, Edinburgh and London.

Chapter 24

Behavior Analysis, Darwinian Evolutionary Processes, and the Diversity of Human Behavior

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The diversity of human behavior stems from three Darwinian evolutionary processes: genetic evolution, cultural evolution, and behavioral evolution. Genetic evolution by natural selection is the paradigmatic example of descent with modification or selection by consequences (Skinner, 1981). Cultural evolution accounts for the diversity of practices across groups and through time (Boyd and Richerson, 1985). Behavioral evolution, the third example of selection by consequences, also called "shaping" of behavior, occurs within the lifetime of an individual, and is a primary focus of behavior analysis.

The science of behavior, or behavior analysis, is properly part of evolutionary biology. It is intimately tied to evolutionary theory in two fundamental ways. First, evolution is the explanation of why behavior and behavioral processes exist at all. It is the only way to understand the peculiarities and constraints that characterize matters like classical and operant conditioning (Baum, 2013). Second, behavioral explanations follow the same mode of explanation as do evolutionary explanations. Skinner (1981) called it "selection by consequences." It may also be called "historical explanation" (Baum and Heath, 1992).

Several writers have suggested that operant conditioning, or behavioral shaping, may be seen as parallel to natural selection. Donahoe (1999) suggests that even Thorndike may have recognized the resemblance between the law of effect and natural selection at the end of the 19th century. Skinner (1953, 1981) stated it overtly and made it the centerpiece to his view of behavior (Ringen, 1999). Gilbert (1970) drew out the parallel at length, and Staddon and Simmelhag (1971; Staddon, 1973) enlarged on it by distinguishing between "principles of variation"—ie, those processes that give rise to behavioral variants—and "principles of selection"—those processes that cause selection among behavioral variants. More recently, Hull et al. (2001), used the term "interactor" to apply both to organisms in genetic evolution and to behavioral units in behavioral evolution, and again compared behavioral evolution to genetic evolution. The parallel is of more than casual interest; it represents a revolution in thought.

POPULATION THINKING

The importance of selection and history has been underappreciated in the study of behavior within the traditions of psychology. One reason is that psychology, like other sciences, was influenced by philosophical views in which the world is thought to be composed of ideal types into which all particulars may be classified. In biology, typological thinking affected the concept of species. In psychology, typological thinking affected the concept of response, the unit of behavior. In biology, typological thinking eventually gave way to population thinking, which is the cornerstone of evolutionary theory and all selectionist theories. The difference between the two ways of thinking may be seen in their views on variation. In typological thinking, variation is "error" and dealt with as a nuisance to be eliminated by averaging. In population thinking, variation is central, and averaging is only an analytic convenience. As Ernst Mayr (1959) wrote, "For the typologist, the type (*eidos*) is real and the variation an illusion, while for the populationist the type (average) is an abstraction and only the variation is real" (p. 2). Arguably, Skinner's greatest contribution to the study of behavior was his

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00024-7

rejection of the typological view of behavioral units (responses). Mayr (1970) observed, "The replacement of typological thinking by population thinking is perhaps the greatest conceptual revolution that has taken place in biology" (p. 5). The same may be said of the (ongoing) revolution in the study of behavior.

From an ontological point of view, a population is an individual—that is, an integral, functioning entity that can change and still retain its identity (Ghiselin, 1997). An individual is a whole with parts—as opposed to a class or category with criteria and instances. An individual changes when its parts change. The parts of a population are its members, and the population changes when its parts change. The population of mice in a particular meadow is an individual and is composed of the mice there. If the proportion of dark-colored mice increases relative to the proportion of light-colored mice, the population has changed or evolved, but it is still the population of mice in that meadow.

Population thinking means the appreciation of populations as units of evolutionary change. Evolutionary theory would be impossible without it. Darwin explained the origin of species by conceiving of species as comprised of populations that change across generations. The idea of change in the composition of a population allowed evolution to be explained as descent with modification, the result of variation with consequences for reproductive success.

The explanation of behavior as an outcome of selection by consequences similarly requires thinking about behavior as comprised of individuals with parts that may change (Baum, 2001, 2004, 2013; Glenn et al., 1992). Only if behavioral change is seen as change in the composition of a behavioral individual may it be explained as descent with modification. The behavioral analog to a population of organisms is an activity, because an activity is an individual with parts that may change when the parts change (Baum, 2002, 2004). A group's pottery manufacturing is an activity with parts like obtaining clay, processing the clay, shaping the clay, decorating the pot, and firing. If, say, the decorations or type of clay changed, the activity of manufacturing pottery will have changed. My tennis playing is an activity with parts like buying equipment, serving, positioning, and returning the ball. My serving may change if I toss the ball in the air differently or swing my racquet differently, and if my serving changes, my tennis playing changes. Behavior analysts think of changes in activities as the result of contingencies between activity parts and phylogenetically important events, and the effect of contingencies is often labeled "selection by consequences" (Baum, 2012; Skinner, 1981).

Taking the unit of change as an individual—population or activity—allows one to think of evolutionary change as descent with modification. To have explanatory power, however, descent with modification or selection by consequences requires identification of an evolutionary process. Plausibility requires construction of specific explanations, which require specific mechanisms (Hull, 1988).

DARWINIAN EVOLUTIONARY PROCESS

A Darwinian evolutionary process includes three basic elements: variation, recurrence, and selection. Each is necessary, and together they suffice to ensure evolutionary change (ie, descent with modification).

Variation

Variation occurs within an individual thought of as a population or pool. A population of mice may be conceived of as a pool of genes, each mouse containing a set of genes, but because of recombination, a pool sufficiently fluid that the individual mice may often be ignored for purposes of explaining change within the population. Within the pool, different genes have different effects. Some influence coat color, some lung capacity, and others the structure of the brain. The key variation within any such pool is the variation among units that affect the same trait but produce different phenotypic effects—for example, that influence coat color but cause coat color to be dark or light. Evolutionary change depends on the existence of substitutable variants. In genetic evolution, such substitutable variants are referred to as alleles. They are substitutable in the sense that one allele may replace another, and they are mutually exclusive in the sense that such replacement is all or none. Evolutionary change consists of change in the relative frequencies of substitutable variants within the pool or population.

The substitutable variants in behavior are the smaller parts of more extended activities, and the total activity over a span of time constitutes the pool. A group's pottery making over the course of a decade may include a variety of styles of decoration, and as time goes by, one of those styles may replace the others, changing the group's pottery making. My tennis serving over the course of a year may include variation in how high I toss the ball, and in time one toss height may prevail, changing both my serving and my tennis playing.

Functional Definition

The units within the pool are defined, not by their structure, but by their function—that is, by their effects. In genetic evolution, the question arises as to how to break the genome into the constituent units that influence phenotype (Dawkins, 1989a). Although DNA has structure, one cannot tell which pieces should be called genes just by examining the structure. According to Dawkins (1989b),

a gene must have three properties: fidelity (faithful copying), longevity (long enough lifetime to be copied), and fecundity (frequent copying). The units that possess these properties, however, may be small or large pieces of DNA, may be contiguous in a chromosome or not, may even be in different chromosomes, and may even be in different organisms [as in Dawkins's example of parasites' affecting phenotypic traits in hosts (Dawkins, 1989a,b)]. Whatever pieces of DNA act in concert to produce the phenotypic effect may be said to be faithfully copied, to endure well enough to be copied, and to be frequently copied to constitute the gene. The alleles compete because they differ in fidelity, longevity, or fecundity. A degree of copying fidelity may be assumed, because it is necessary for transmission. Differences in longevity and fecundity, however, result from differences in the alleles' phenotypic effects. A darker coat color may increase its possessor's likelihood of surviving long enough to reproduce.

Phenotypic effects, though often thought of as effects on morphology, are better seen as effects on the environment (Dawkins, 1989a). A darker coat color affects the ability of predators to detect a mouse against the ground. All phenotypic effects are environmental effects, because they facilitate exploitation of resources, survival, or reproduction. The point becomes clearer if we focus on genetic effects on behavior. Building a better nest alters the environment of the nestlings. Dawkins uses the example of the beaver's dam construction, which creates the beaver pond and reduces risk of predation, and has a host of other good effects on the beaver's environment. Human beings change their environment in myriad ways, creating shelters, places for plants to grow, instructional institutions, and so on. All may be seen as effects on the environment that function (usually) to enhance exploitation of resources, survival, and reproduction.

This focus on function, in the form of environmental effects, solves what would otherwise be an intractable problem: how to define genes. In a broader view of selection by consequences, it solves the problem of defining the substitutable variants within the pool of variants.

The same problem of defining units arises in cultural evolution and in the evolution of individual behavior, both of which constitute Darwinian evolutionary processes. As a focus on the structure of DNA offers little guidance about the definition of genes, so the structure of cultural practices and individual operant activities tells little about how they should be defined. Not that structure is totally irrelevant; in all three processes, structure constrains the definitions. DNA sequences specify the ordering of strings of amino acids, different configurations coding for different amino acids. Cultural practices and individual activities divide along what Skinner (1938) called "natural lines of fracture" (p. 33), constrained by anatomy and arrangements in the nervous system. As the codons of DNA represent "natural lines of fracture" and specify minimal units that may be aggregated into genes, so fixed-action patterns and the structure of bones and muscles constrain what may be aggregated into the substitutable variants of culture and individual operant behavior (Skinner, 1969). The making of a pot comprises motions of the fingers and hands, but only those motions that the structure of the fingers and hands allows. The physical motions, however, are little help when it comes to defining the evolutionary unit. That will be the making of a certain kind of pot, and the substitutable variants will be the making of other kinds of pot, some of which may leak less, may be easier to handle, or may serve a social function by virtue of design. These variants compete within the culture pool, just as alleles compete within the gene pool.

All three units—genes, cultural practices, and individual operant activities—are defined in terms of environmental effects. All three are defined by what they accomplish in the world with which they make contact. Dawkins (1989a) made this clear about genes in his discussion of "extended phenotype." Guerin (1997) clarified the point for cultural practices when he argued that the functional unit of culture is "getting a job done." Every culture comprises "jobs" that must get done. At the most general level, the jobs might be reproduction, obtaining resources, protection from weather and enemies, and maintaining group cohesion. These general jobs subsume more specific jobs, such as child rearing, transport, and ownership. Whatever the level of generality that suits the analysis of culture, the substitutable variants will be different ways of getting the same job done. Different ways of raising children, of transporting oneself and goods, or of demonstrating group membership may compete with one another and may differ in their outcomes. Skinner (1938, 1953, 1957) explicitly defined operant "responses" (activities here) according to their environmental effects. One might say, following Guerin (1997), that a rat's lever pressing gets a job done. Although depression of a lever constitutes a discrete unit of behavior, more extended patterns produce more extended results. In the laboratory, several presses may be required for a bit of food, constituting a larger unit. In the everyday world, extended accomplishments always entail more specific accomplishments. Helping an unhappy customer entails listening to the complaint, making suggestions, talking to suppliers, and so on. Making a living might entail finding a job, going to work every day, specifying one's duties, and so on. Giving directions entails various utterances—statements about location, queries, and descriptions of action. Different ways of helping the customer, of making a living, or of giving directions constitute substitutable variants that may compete and may differ in their results. A customer may come away more satisfied, one may make a better living, and directions may be given more clearly.

Pooling

All three processes, genetic, cultural, and behavioral evolution, require a pool of variation that includes substitutable variants. In general, the pool generates a frequency distribution—a profile of the frequencies of various types—that may change with time. For talking about evolutionary change, the important relative frequencies are those of the substitutable variants. Change results from competition. Fig. 24.1 illustrates the general idea. The top diagram represents a hypothetical pool, within which are substitutable variants A, B, C, and D, which occur at different frequencies. They could represent four different alleles for four different structures of an enzyme, or four different ways to catch termites (eg, with fingers, with a leaf, with a stick, or with a leaf stem). The relative frequencies are shown in the middle graph (open bars; the shaded bars will be discussed later). Allele (variant) B occurs at the highest frequency, then C, then D, and the least frequent is allele A. This pattern of relative frequencies may remain stable with time or may change, depending on selection.

Whereas the middle panel of Fig. 24.1 assumes discontinuous variation, the open bars in the bottom panel illustrate a hypothetical frequency distribution for variation fine enough to be considered continuous. It could represent variation in the genes affecting height or variation in squeezing clay that affects the thickness of the walls of pots. Although the variants cannot be grouped into discrete categories, they still exhibit a pattern of frequencies that may remain stable or change, depending on selection.

Fig. 24.1 illustrates the general idea of a pool characterized by a pattern of frequencies, which constitutes the essential element of variation in any Darwinian evolutionary process. Genetic evolution, cultural evolution, and behavioral evolution (shaping) all assume such a pattern of variation, although they differ in details, such as whether the units are localized or extended and whether variation is continuous or discontinuous. Genes are usually thought of as particular locations on chromosomes (ie, localized units) and alleles as differing in physical structure (ie, varying discontinuously), but when enough genes act in concert and vary, the substitutable variation becomes (approximately) continuous. Under some circumstances, such as parthenogenesis, the unit of variation may even be the entire genome (Dawkins, 1989a). Then the substitutable variation is certain to seem continuous. Although Dawkins (1989a,b) suggested a discrete unit of cultural variation analogous to the gene, the meme, nothing requires that the units of culture be localized or that variation in culture be discontinuous, any more than in genetic evolution. Boyd and Richerson (1985), for example, describe mathematical models of cultural evolution that assume variation to be

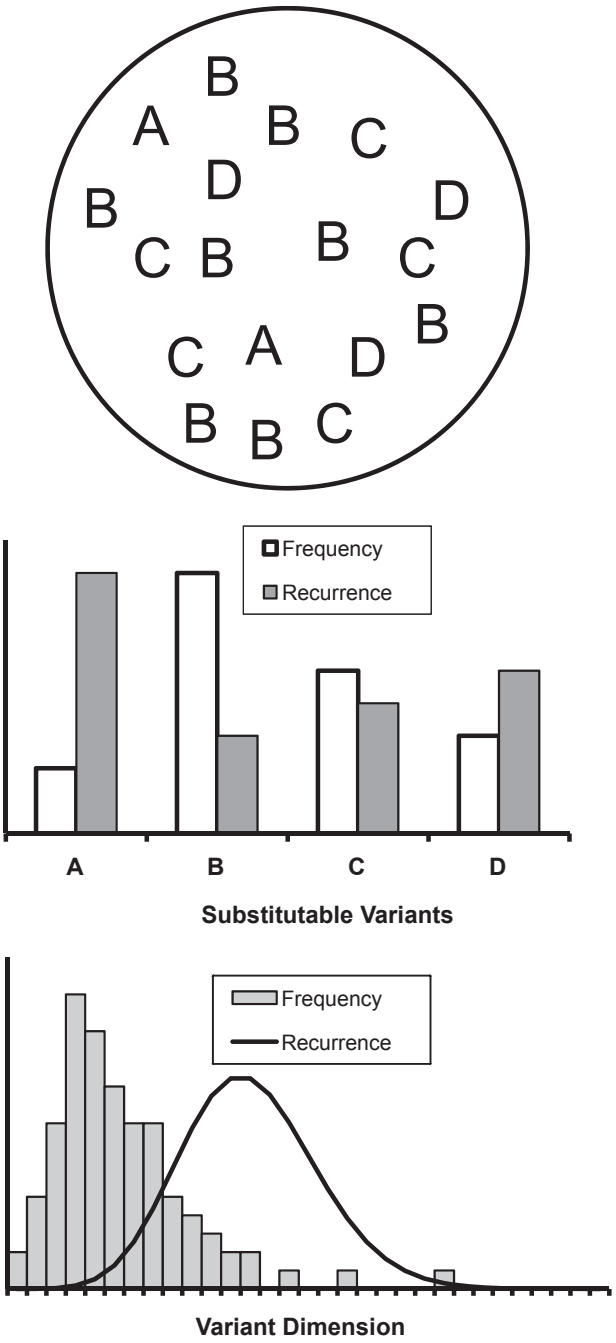

FIGURE 24.1 Population, frequency, and recurrence. Top: a population with four substitutable variants, A, B, C, and D. Middle: Frequencies and recurrences of the variants. Bottom: Frequency and recurrence with continuous variation.

continuous. In her classic book, *Patterns of Culture*, the anthropologist Ruth Benedict (1934) described the patterns of behavior in culture with the word "custom." A custom or a practice cannot be localized to particular moments of time; it is an extended pattern of behavior that can only be observed over a substantial period.

With individual operant behavior, too, we are under no compulsion to assume discontinuous variation or localized units. That variation may be continuous is recognized in the study of response dimensions such as force, duration, and rate. The assumption that behavior must be defined in terms of momentary response units, however, has persisted for over 100 years. Nineteenth-century connectionism, in the forms of associationism and reflexology, promoted a view of behavior as composed of localized units such as ideas, sensations, and responses. That view was an accident of history, however, and may be overcome. Baum and Rachlin (1969), for example, suggested that behavior be divided into periods filled with various activities. Favorite responses of the laboratory, such as the lever press and the key peck, may be recast as activities, lever pressing and key pecking, which extend in time (Baum, 1976). Rachlin (1994) suggested that behavior generally be thought of as organized into patterns extended in time (Baum, 1995a, 1997, 2002, 2004, 2013). As with the customs of culture, an individual's daily behavior may be divided into activities like working, attending to family, and entertainment, none of which may be localized to moments in time.

Frequency distributions like those in Fig. 24.1 presuppose that one may characterize the variation in a gene pool or behavior pool by taking a sort of snapshot of the frequencies at a moment in time. This might seem necessary for analytical purposes, because the frequencies may be changing. In practice, however, the snapshot is an abstraction, just as instantaneous velocity in physics is an abstraction, because any real sample is extended in time. In a gene pool, birth and death constantly alter the picture. For a behavioral pool, temporal extension is unavoidable. The customs of a culture or the habits of an individual cannot occur at a moment in time. The problem of taking a "snapshot" of frequencies is solved by choosing a time period long enough to provide an adequate sample but short enough that the pool may be thought of as unchanging for that duration. Depending on rate of change, one might gather data over a period of weeks, months, or years. As long as change in the pattern of frequencies during a period of sampling is negligible in comparison with change between samples, the course of change in the pool may be studied. That population thinking is central to genetic evolution has long been recognized. Population thinking, however, is equally central to understanding evolution of cultural behavior and individual operant behavior (Glenn et al., 1992; Hull et al., 2001).

Cultural Practices and Individual Operant Behavior

The line between cultural practices and operant behavior patterns may be fine. Indeed, Skinner (1981) argued that cultural patterns are operant patterns. Since cultural practices presumably are maintained by their consequences, they might be considered operant patterns by definition. They may be distinguished, however, for the purpose of discussing cultural evolution by two characteristics. First, cultural practices are the possession of a group. To be called a cultural practice, a behavior pattern must occur in the members of a group—possibly a subgroup within a larger group, but definitely in more than one individual. Second, cultural practices are transmitted from member to member in the group. Unlike individual operant patterns, which one may say are transmitted to the same individual at different times, cultural practices are transmitted from one individual to another and may occur in different individuals at the same time.

Recurrence

Recurrence means "occurring again" or "coming up again." It is a general term for the tendency of a type of unit to reappear, with variation, time after time in the population—a more general term than "replication," "transmission," or "retention" (Baum, 2001; Campbell, 1965).

The "Copying" Metaphor

Genetic evolution is usually taken as the paradigmatic example of a Darwinian evolutionary process. As a prototype, genetic evolution has both advantages and disadvantages. An advantage is that it has received enough attention to be both familiar and relatively well understood. A disadvantage is that, being comparatively well understood, some of its peculiarities are too easily mistaken for properties of evolutionary processes in general. This is particularly true of its mode of recurrence, which is often described with the metaphor of "copying."

Evolutionary recurrence need little resemble copying a page in a photocopier. The word "replication" may be a synonym for copying, but may also be equated to reconstruction, which, for DNA, would be closer to the mark. We know about the uncoiling of the strands and the assembling of amino acids into replicate strands, with some recombination and occasional errors. In meiosis, the entire genome is replicated and divided into haploid components at once. The entire haploid genome is passed as a whole to the next generation. We need to ask, however, which properties of genetic transmission are essential for evolution. Darwin knew nothing of what we know about genetics today. Yet he was the author of the theory of evolution. His ignorance of genetics in no way prevented him from seeing the role of recurrence.

Darwin understood what was necessary: that the traits of parents tend to recur in offspring. More generally, the traits of one generation are passed on to the next generation. Even the words "parent," "offspring," and "generation"

impede generalization. The essential part is recurrence through time. Traits tend to "breed true." In the gene pool of a population of mice, the genes that make for a dark coat tend to recur through time, with the result that dark coats tend to recur (and possibly lower predation rate). In the beavers' gene pool, the genes that make for dam constructing tend to recur, and if substitutable variants exist, each variant tends to recur, although selection may favor one variant over others. True, the recurrence of genes is the result of the details of reproduction, and those details are essential to understanding many aspects of genetic evolution. For a general definition of evolutionary process, however, what counts is the tendency of types in a population to recur in time.

Today we forgive Darwin for having believed in the inheritance of acquired characteristics, but writers about culture point out that such inheritance does occur in cultural evolution (eg, Boyd and Richerson, 1985). Again, however, the mechanism of recurrence is only important for understanding the details of cultural evolution. That it entails the inheritance of acquired characteristics helps us to understand the ways in which cultural evolution differs from genetic evolution. It is faster, for example, because transmission may occur between any individuals, not just parents and offspring, and may occur throughout the lifetime of an individual. It occurs as a result of imitation and instruction, although we might argue about exactly what those processes entail (Baum, 2000, 2005). The key, however, is that if a potter makes a certain kind of pot, his students will make the same kind of pot, and their students also, and so on. The practice recurs through time in the culture's pool of practices.

Suppose, instead of genetic evolution, we took behavioral evolution (ie, shaping) as the paradigmatic example of an evolutionary process. We would see immediately that copying or replication is just one means of recurrence. A pigeon in an experiment pecks at a key time after time. A person goes to work day after day. Too little is known about the nervous system to say what the mechanism is by which behavior recurs in the same organism from time to time. Luckily, we may proceed with studying behavior without having any idea how recurrence is accomplished. The situation resembles that in biology prior to the synthesis of genetics with evolution in the early part of the 20th century.

Imperfect Recurrence

Part of the reason for variation is that recurrence is often imperfect. Hull (1988) defines a replicator as "an entity that passes on its structure largely intact in successive replications" (p. 408). A paraphrase for the sake of generality might substitute "recurrences" for "replications." Emphasis, however, should fall on the word "largely." Accidents happen. In genetic evolution, reconstruction of DNA sometimes goes awry. In cultural evolution, imitation and instruction may be inexact. In behavioral evolution, too, variation is intrinsic to recurrence, because context never exactly repeats, reconstruction even of a stereotyped activity like key pecking varies, and accidents happen. Recurrence need only have high fidelity; it need not be perfect. Indeed, one might argue that it must be imperfect, if the pool is to include sufficient variation to produce novelty. Without novel types, a pool's response to selection must eventually cease.

Recurrence in Behavior

In genetic and cultural evolution, the units (genes or practices) may outlive their possessors (their "vehicles" in Dawkins's (1989b) parlance; their "interactors" in Hull's (1988)). Individual operant behavior, in contrast, must die with its possessor—by definition, because if it lived on in others, it would be considered cultural. In no way, however, does this disqualify behavioral shaping as an evolutionary process. The key elements remain: a pool of variation, substitutable variants, and recurrence of variants through time. The frequency distributions in Fig. 24.1 might describe genetic variation, cultural variation, or behavioral variation. Whether they remain stable or change with time depends on their relation to selection.

Selection

The key to selection is differential recurrence. If substitutable variant A1 tends, on the average and over time, to recur more frequently than A2, the relative frequency of A1 increases at the expense of the relative frequency of A2. This happens if the size of the pool of variants is fixed or increases more slowly than the variants' rate of recurrence. Usually one assumes the pool size to be fixed, because the size of a population of mice, for example, is limited by the environment's carrying capacity—that is, the resources available to support the population. A behavioral pool, of cultural variants or individual behavioral variants, is fixed by limits on time, because only so much behavior can occur in a 24 h day. Consequently, when one substitutable variant increases in frequency, another must decrease. If one variant is more successful, it tends to replace the other.

One substitutable variant succeeds over another by virtue of superior environmental effects. For genetic evolution, this is where longevity and fecundity come in. Genes endure if their vehicles (interactors) endure, and recur if their vehicles (interactors) reproduce. The specific reasons for enhanced recurrence may be extremely varied—better defending or capturing of resources, better avoidance of predators, better defense against parasites, better mate selection, more mates, more offspring, better

care of offspring, and so on. All of these superior environmental effects ultimately increase the recurrence of the alleles that produce them and thus decrease the recurrence of the less successful alleles. For cultural and behavioral evolution, the same sorts of environmental effects act on the pool, but less directly and, therefore, with some slippage.

Selection in Culture

The consequences of cultural practices that vary, making one variant more successful than another, may be thought of as reinforcers and punishers. Practices are maintained proximally by social reinforcement and punishment (Baum, 1995b, 2000, 2005; Skinner, 1981). "Our group shuns the eating of pork" is backed up with punishment (eg, disapproval, ostracism) for eating pork. "This mode of adornment is correct" is backed up with reinforcement (eg, status, mating opportunities) for adorning oneself so. Ultimately, the maintaining and differentiating social reinforcement and punishment are cashed out in terms of reproductive success of the vehicles (interactors) that carry the genes producing susceptibility to social consequences ("docility"; Simon, 1990). If group membership is beneficial to reproductive success, then group cohesion and cooperation are beneficial, and practices that make for group cohesion and cooperation are selected as a result of the members' docility—their susceptibility to social consequences. Indeed, Boyd and Richerson (1992) demonstrated theoretically that social punishment allows selection of cooperation and just about any other behavior salutary to the group. [This summary omits other adaptations, such as sensory specializations and imitation (Baum, 2000, 2005).]

Dawkins (1989b) argued that the slippage between proximal social consequences and ultimate reproductive consequences allows cultural evolution to proceed independently of genetic evolution. The logic of genetic evolution goes against such a view (El Mouden et al., 2014). If some alleles make for more docility than others, the most successful alleles lie somewhere in the middle of the range of possible levels of docility, somewhere between none and "anything goes." Too much docility means too little certainty of reproduction, because too much docility allows the spread and maintenance of customs that reduce reproduction. Thus, ultimately, alleles producing too much docility are selected against. (Boyd and Richerson (1985) make a similar point in their discussion of the tension between imitation and individual learning.)

One factor that curbs docility is primary reinforcement and punishment. As Dawkins (1989b, p. 57) suggests, consequences like "sweet taste in the mouth, orgasm, mild temperature, smiling child" or "various sorts of pain, nausea, empty stomach, screaming child" may have a genetic base because their presence generally affects the likelihood of successful reproduction. Such stimuli constitute proximate tokens of ultimate reproductive success or failure, called elsewhere phylogenetically important events (PIE; Baum, 2005, 2012). If an interactor (vehicle) could be put together that would increase any behavior that produced the good environmental effects (circumstances that enhance reproductive success) and avoided the bad environmental effects (circumstances that depress reproductive success), such an interactor (vehicle) would prosper, and genes it carried would be more likely to recur in subsequent generations. As a result, genes that make for susceptibility to reinforcement by fitness-enhancing PIEs are selected. As a result, neither individual behavior nor cultural customs will stray too far from patterns that maintain the frequency of those PIEs. They will stray, however, for two reasons. First, the PIEs' bearing on reproductive success is far from certain. Sweet taste is a reinforcer, and some consumption causes no problems, but overindulgence in sweets undermines health. Second, PIEs may conflict with one another. The same behavior that produces a smiling child may also produce an empty stomach. Which should win out may be far from clear; only the calculus of long-term reproduction can tell. When short-term and long-term consequences conflict this way, dysfunctional behavior may arise (Baum, 2016; Rachlin, 1995). Whether it persists or not depends on whether patterns that enhance fitness in the long run, such as eating fruits and vegetables, replace the dysfunctional ones, such as eating junk food (Baum, 2000, 2005, 2015; Rachlin, 1995). Although a person may die before dysfunctional behavior is replaced, correction in culture lies under no such limitation. It may take a few generations.

Primacy of Reproductive Success

Maladaptive customs tend to drop out of the culture pool for two reasons: first, because failure to correct results in natural selection. Those who overindulge in sweets tend to become sick with diabetes and leave fewer offspring as a result (Diamond, 1992). Maladaptive customs decrease in frequency when their vehicles (interactors) leave fewer descendants to continue the customs. Groups that follow dangerous or abstinent practices, such as Quantrill's Raiders or the Shakers, tend to disappear. Second, but probably more important, is that maladaptive customs contrast with their competitors (substitutable variants) in the calculus of reinforcement and punishment—ie, in the tokens of fitness. Prohibition in the United States was a response to the ruinous effects of overindulgence in alcohol; today educational campaigns encourage patterns of moderation or abstinence, based on better quality of life. When a maladaptive custom like smoking tobacco spreads through a culture because of short-term reinforcement, its long-term punishing effects eventually come into focus in

the form of social contingencies that punish it more immediately (or reinforce alternatives like nicotine patches more immediately).

The power of reinforcers and punishers as tokens of long-term reproductive success makes persistence of maladaptive customs unlikely. The genetic underpinnings of reinforcement and punishment argue against Dawkins's (1989a,b) conjecture that cultural evolution proceeds independently of genetic evolution. The genes that underlie learning and culture open the door, so to speak, to environmental influence, but they do not fling it wide.

Selection in all three processes—genetic, cultural, and behavioral evolution—may be traced back to reproductive success of genetic variants. In genetic evolution, the relation is direct; in cultural and behavioral evolution, the relation is less direct, but still present. When genes that make behavior sensitive to its consequences are selected, that must mean that the advantages of behavioral flexibility outweigh the costs it imposes in terms of energy and risk of error. If not, competitor genes that allow less flexibility would prevail. So, tokens of reproductive success (PIEs) attain the status of reinforcers, because variation in the environment rewards flexibility in the means to them. Signs of health, resources, and social relationships became powerful reinforcers, because the interactors (vehicles) for which they were reinforcers reproduced more often. A parallel argument applies to punishers, such as nausea, pain, snakes, and frowns. The same mechanisms of reinforcement and punishment that select among substitutable variants in behavioral evolution select also in cultural evolution. The differences are that cultural evolution entails transmission from individual to individual—imitation and instruction—and therefore depends heavily on social stimuli for provenance, and social reinforcement and punishment for selection.

In all three of the processes we are discussing, a question arises about the extent of the vehicles or interactors. Hull (1988) defines an interactor as "an entity that interacts as a cohesive whole with its environment in such a way that this interaction *causes* replication [ie, recurrence] to be differential" (p. 408; italics in the original; bracketed material added). But how large a unit can interact as a "cohesive whole"? Group selection has been treated with skepticism among evolutionary biologists, because it should normally be too weak to have much effect on gene frequencies. To work, it would require that gene flow into the group be negligible. That might be true of colonies of eusocial insects, for example (Seeley, 1989), but it would be unlikely for most groups, because of immigration of new members into the group. In cultural evolution, group cohesion is more likely, because imitation and instruction maintain a high degree of conformity within the group, even if new members join (Boyd and Richerson, 1992). In cultural group selection, groups with certain practices (eg, a type of food cultivation or cooperation in obtaining resources) may out-compete other groups. The advantaged group may increase in frequency if it reproduces by fission and if competing groups tend to dissolve.

In evolution of individual operant behavior, where the distinction between replicators and interactors disappears, the analog to group selection is the temporally extended contingency. Extended contingencies are often discussed in terms of delays of reinforcement. The more temporally extended the behavioral pattern, the more delayed the consequences. Alternatively, one may consider delay to be incidental and the crucial aspect of extended patterns to be their cohesiveness. Extended behavioral patterns, such as eating a good diet, are notoriously difficult to maintain. Rachlin (1995) argues that good extended patterns (often called "self-control") have a greater long-term payoff than short-term patterns (called "impulsiveness" or "defections" from the larger pattern). A defection from eating a good diet—eating an ice cream sundae—has an immediate payoff, but poorer consequences in the long run than eating a good diet (Baum, 2016). Selection on extended patterns is weak for the same reason that group selection on genes is weak. The boundaries of the group or of the extended pattern tend to be permeable—to immigration or to defection—the greater the permeability, the weaker is selection. This may be overcome in behavioral evolution by introducing relatively short-term contingencies that maintain the extended pattern intact (eg, reminders about one's diet).

Why not Phenotypic Plasticity?

To explain the variation of culture or behavior from one environment to another, the alternative to selection is phenotypic plasticity. Cosmides and Tooby (1992) and Tooby and Cosmides (1992), for example, put forward the idea that the human brain contains a large number of "modules," "algorithms," or "mechanisms" that produce behavior depending on environmental conditions. They contend, "If human thought falls into recurrent patterns from place to place and from time to time, this is because it is the expression of, and anchored in, universal psychological mechanisms" (p. 216). They refer to such patterns as "evoked culture." The conception has been compared to a jukebox containing recordings that can be played whenever called upon (Wilson, 1999). When food availability is highly variable, the "social contract algorithm" plays out food sharing; when food availability is stable, the jukebox plays keeping food within the family. Such explanations fail on two grounds. First, they are implausible. They exaggerate what is probably true, that genes constrain evolution of cultural practices and of individual behavior, to make a claim that would skip over the obvious effects of consequences on behavior. Instead of sensitivity to

feedback, they substitute input–output rules; given a certain environmental input, the mechanism produces a certain output. Such a view fails to explain an obvious fact: that culture evolves even if the environment remains constant. Second, alternative explanations are more plausible. If human behavior "falls into recurrent patterns," that may be because of convergent cultural or behavioral evolution. Similar contingencies select similar behavior.

Price's Equation

George Price (1970, 1972) derived an equation, using straightforward algebra, that expresses precisely the meaning of natural selection. Imagine a population or group of N members at two time periods or "generations." A trait or property of these members x varies among them. The trait could be the presence ($x = 1$) or absence ($x = 0$) of a particular allele ($x = 0$, 0.5, or 1.0 for diploidy), or a quantitative trait like body size or coloration. At Time 1, the mean of x across individuals is $\overline{x}$. Each individual i contributes w_i surviving offspring to the population at Time 2—i's fitness or recurrence. Define a variable v_i that equals $w_i/\overline{w}$, the relative fitness of i. Each v_i is a weight; their sum equals N and their mean equals 1.0. The mean of x at Time 2 $\overline{x}'$ equals:

$$\sum_i v_i x_i/N + \sum_i v_i \Delta x_i/N,$$

where Δx_i is the change in x_i for member i from Time 1 to Time 2 due to imperfect fidelity of recurrence. Using the definition of covariance $\left(\sum_i v_i x_i/N - \overline{v}\overline{x}\right)$, and taking the difference, $\Delta\overline{x} = \overline{x}' - \overline{x}$ leads to the simplest form of the Price equation (see Price (1970) and McElreath and Boyd (2007, Chapter 6) for more detail):

$$\Delta\overline{x} = cov(v_i, x_i) + E_v(\Delta x_i). \quad (24.1)$$

Eq. (24.1) says that the mean change in x equals the dependence of relative fitness on x_i plus an expected value that gives the mean change in x apart from the covariance. The covariance represents selection; if relative fitness varies positively with x_i, $\Delta\overline{x}$ is positive, and the trait increases in the population. If the covariance is negative, the trait decreases, and if the covariance is zero, the trait remains stable. The second term on the right, which expresses the tendency of x to change as it recurs from Time 1 to Time 2 due to factors usually rare or negligible (eg, mutation or meiotic drive), may be considered close to zero for genetic evolution.

Put in more general terms, Eq. (24.1) says that if recurrence is differential with respect to various levels of a trait and fidelity of recurrence is high, then the trait recurs increasingly (positive covariance) or recurs decreasingly (negative covariance) in the population. Since the equation is an identity, it describes rather than predicts, but it is a valuable analytical tool for thinking about selection—for example, group selection.

Suppose that the group under consideration is one group among many, because the population is structured into groups. Since Eq. (24.1) does not depend on the sort of individuals, Eq. (24.1) would also apply to selection among groups. For the sake of clarity, we index groups with the subscript g and apply Eq. (24.1) to get an expression defining $\Delta\overline{x}_g$ the change in average fitness of the group. The equation says that if the covariance between levels of x_g and relative fitness v_g is positive, a group with a higher mean of x increases in x and grows in size relative to other groups. For example, if darker coloration is advantageous in avoiding predators, a group with darker coloration will grow and become darker.

In applying Eq. (24.1) to group selection, however, the second term on the right, $E_v(\Delta x_g)$, is no longer negligible, because the change in x_g apart from group selection includes changes in individual members due to selection at the level of individual members. Recognizing that x_g is a mean across members in the group that may change from Time 1 to Time 2, we treat Δx_g the same way we treated Δx and arrive at:

$$\Delta\overline{x} = cov(v_g, x_g) + E_g\left[cov(v_{ig}, x_{ig}) + E_v(\Delta x_{ig})\right], \quad (24.2)$$

where the subscript ig indicates member i in group g (see Henrich (2004) and McElreath and Boyd (2007, Chapter 6) for more detail).

The right-hand side of Eq. (24.2) has two components: one for selection between groups and one for selection between members within groups, the expected value term. For genetic evolution, we may ignore the expected value of Δx_{ig} in Eq. (24.2) as we did the expected value of Δx_i in Eq. (24.1), because the change would be due to rare or negligible factors such as meiotic drive and mutation. Eq. (24.2) then simplifies to the sum of a covariance for between-group selection and expected value of covariance for within-group selection.

An alternative form of the Price equation that uses the algebraic relation between covariance and the regression coefficient β may further clarify understanding of group selection (see Henrich (2004) and McElreath and Boyd (2007, Chapter 6) for more detail):

$$\Delta\overline{x} = \beta(v_g, x_g)var(x_g) + E\left[\beta(v_{ig}, x_{ig})var(x_{ig})\right]. \quad (24.3)$$

Eq. (24.3) makes clear that the dependence (β) between v and x and the variance in x must both be greater than zero for selection to occur. Each term on the right implies a role for each of the three ingredients of evolution: variation ($var(x)$), selection (β), and recurrence (v).

When applied to genetic evolution, Eq. (24.3) clarifies why genes for altruistic and cooperative behavior are unlikely to be selected by genetic evolution on its own. Some

traits may have both between-group and within-group components that act in concert—both have positive β—such as body size (helpful in intergroup combat) or tendency to stay close to the rest of the group (avoiding predators). Genes for altruism or cooperation, however, though helpful for the group, tend to reduce the fitness of individuals that behave so. Thus, β is positive for between-group selection, but negative for within-group selection. Since variance across groups $var(x_g)$ in particular is lowered by migration between groups, the groups have to be practically completely isolated for group selection to overcome negative individual selection. Since negative β is likely to be high for any individual incurring an immediate cost for helping or cooperating with strangers, and within-group variance $var(x_{ig})$ is unlikely to be zero, even a small amount of migration between groups will ensure that between-group selection is smaller than the within-group selection, making $\Delta\overline{x}$ negative.

Eqs. (24.1)–(24.3) may be applied to cultural evolution, too, with suitable changes in definition. A cultural practice that might be considered all or none (eg, allowing marriage between first cousins or not, eating pork or not, and primogeniture or not) would take the place of an allele that is present or not. As with genetic evolution, however, quantitative variation in a practice (eg, a ritual performed daily or less often, for longer or shorter duration, with more or less of some ingredient, etc.) would do just as well for the variable x.

Recurrence of a practice from Time 1 and Time 2 goes, not just vertically as in genetic evolution, but obliquely and horizontally also (Boyd and Richerson, 1985; Richerson et al., 2016). Teachers, coaches, ministers, and peers both model practices and instruct practices that have proven successful in gaining the proximate tokens of ultimate fitness (reinforcers and avoidance of punishers). Particularly if these influential people are prestigious and display the trappings of success, this modeling and instructing spur the recurrence of the practice at Time 2, denoted, as before, w_i. As before, too, v_i is relative recurrence, $w_i/\overline{w}$, and if covariance between v_i and x_i is positive, the practice spreads. The second term on the right might be considered nonnegligible if one wished to incorporate errors on the part of recipients, but usually may be considered negligible because errors would likely be insignificant compared with selection (see El Mouden et al. (2014; supplemental Document S1) for a detailed derivation of Eq. (24.1) for culture and further discussion).

Eq. (24.1) would be about the spread of a practice through a cultural group. If we think of cultural groups as parts of a larger population, they may compete with one another for resources and members. Eqs. (24.2) and (24.3) will apply, with the same changes in meaning of the variables. Eq. (24.2) contains the same two components of intergroup selection and within-group selection (El Mouden et al., 2014; Henrich, 2004). If a cultural practice benefits the group, and the more members practice it, or the more members' increased x_g increases the prevalence of x_g in the group (v_g), the more positive is the first term in Eq. (24.2). Whether the covariance in the second term is positive or negative depends on whether it is beneficial or harmful to the individual who engages in the practice.

To understand how an altruistic or cooperative practice can spread in a population, Eq. (24.3) shows what happens if the within-group covariance for members is negative. As with genetic group selection, the variances $var(x_g)$ and $var(x_{ig})$ are crucial. In cultural group selection, biases in imitation and instruction ("transmission biases") that promote conformity lower $var(x_{ig})$ to near zero, even in the face of considerable immigration between groups. For example, if immigrants into a group tend to adopt the practice that is most frequent or above average in the group or tend to adopt the practice of prestigious or successful group members, their conformity will keep $var(x_{ig})$ low (Henrich, 2004). Thus, the cost to the individual represented by the negative covariance of the second term may be offset by the positive covariance for the group, and altruistic and cooperative practices can spread in the population. The group in which members sacrifice for the group will gain more resources than other groups and will increase in numbers at the expense of other groups (Henrich, 2004).

Eq. (24.2) represents "multilevel" selection, but just at two levels—groups and individuals (McElreath and Boyd, 2007, Chapter 6). A practice may have many parts, and some of these parts may change without the practice taking on a new identity. For example, a manufacturing process or a ritual may drop or add elements; the American Pledge of Allegiance after many years changed to include the words "under God," but it is still the Pledge of Allegiance, and process improvement constantly upgrades manufacture of automobiles, but the practice remains the manufacture of automobiles (Baum, 2002). When practices change in their parts, one might consider a third level of selection: within-practice selection. In Eq. (24.2), Δx_{ig} may be treated as change due to competition among alternative parts within the practice and expanded as before to result in a three-term Price equation (McElreath and Boyd, 2007, Chapter 6).

As far as I know, no one has applied Price's equation to behavioral evolution. The entities that may vary would no longer be individual organisms, because we are dealing with the behavior of a single organism. The varying entities are time samples within a larger time interval that constitutes the population—seconds within a minute, minutes within an hour, hours within a day, weeks within a year, and so on (Baum, 1973, 2012). The variable x_i that differs across time samples may be occurrence or not of an activity, if the time samples are short, or rate or time taken up

by the activity, if the time samples are longer, or any other quantitative aspect of an activity. The mechanism of recurrence is induction, which for operant activities is based on positive covariance with reinforcers and negative covariance with punishers (Baum, 2012). Eq. (24.1) applied to behavioral evolution means that if time samples (indexed by i) including more of an activity in Time Interval 1 correspond to relatively more such time samples in Time Interval 2 (ie, positive covariance with v_i in Eq. (24.1)), then the activity ($\bar{x}$) increases from Time Interval 1 (Population 1) to Time Interval 2 (Population 2)—$\Delta\bar{x}$ is positive. In a laboratory example, if a rat's rate of lever pressing is measured in 2 min intervals, the rate varies and may increase from 1 h to the next (Baum, 2012, Fig. 17). If a person's life changes by having children, spending more time with family daily in a period (population) of a month may vary positively with relative recurrence v_i in the next month, and the amount of time spent with family increases from month to month.

As with cultural group selection, Eqs. (24.2) and (24.3) apply to operant activities at a level or time scale of selection that may include selection at a lower level or shorter time scale. Cultural practices are, after all, operant activities. In an ontological perspective, operant activities and cultural practices are individuals with parts that work together to serve a function (Baum, 2002; Ghiselin, 1997). The analog to group selection is selection of whole activities extended in time, like playing tennis well or poorly and relating to one's spouse well or poorly. The analog of within-group selection is the selection of parts referred to earlier, because every activity is composed of parts that are themselves activities on a smaller time scale (Baum, 2002, 2012; Baum and Davison, 2004). Thus, the second term in Eq. (24.2) for behavioral evolution represents selection among parts of an activity. A tennis player's serve may improve when the ball is thrown up in a new way, and that variant may be selected. Active listening may improve one's relationship with one's spouse and be selected to replace a passive stance.

Eq. (24.3) for behavioral evolution illuminates problems in self-control, including altruism and cooperation. The conflict between impulsivity and self-control translates into a positive first term on the right (self-control) and a negative second term (impulsivity). Avoiding a bad habit or cultivating a good habit (eg, refusing a drink or a piece of cake or visiting the dentist) entails the cost of forgoing immediate enjoyment or of immediate discomfort, whereas the extended pattern (x_g; sobriety, dieting, or good health) has positive β, but the positive β must suffice to offset the negative β of the second term (for x_{ig}). This offsetting may occur if $var(x_{ig})$ is reduced to zero by following a rule that enforces good behavior (refusal of the drink or cake; doing the right thing) on particular occasions. Seen this way, altruism and cooperation are examples of good habits with immediate cost and long-term benefit (Baum, 2016; Rachlin, 1995, 2002).

Price's equation is incomplete or limited in two ways. First, it relies on linear regression (Price, 1970). The full-range relation between x_i and v_i may be nonlinear; often it will approach an asymptote, because a stable level of x in a population, due to dominance or frequency-dependent selection, will go along with reduced variance in v_i. When the population reaches equilibrium, the covariance between v_i and x_i disappears. Thus, Price's equation only has meaning when a population is in the process of evolving and we consider a limited range of x_i over which the relation between v_i and x_i is approximately linear. It doesn't apply to the whole process of change toward equilibrium. Second, by focusing on one particular allele, trait, or variable, the equation ignores the fate of other, competing variants. In all three evolutionary processes, if one variant increases, usually others must decrease. Competition implies a limit—carrying capacity for genetic evolution, fixed or slowly growing population for cultural evolution, and fixed time interval for behavioral evolution. A complete picture requires considering the fates of all the substitutable, competing, variants.

EVOLUTIONARY EXPLANATIONS OF BEHAVIOR

Mayr (1961) distinguished between proximate and ultimate explanations of behavior. Alcock (1993) incorporated the distinction into a textbook on animal behavior. According to Alcock, proximate explanations explain "how mechanisms *within* an animal operate, enabling the creature to behave in a certain way" (p. 2; emphasis in the original). Ultimate explanations explain how those mechanisms evolved as a result of selection. Proximate explanations refer to physiology and development. Ultimate explanations refer to history and reproductive success.

Genetic Proximate and Ultimate Explanations

Proximate explanations are about individual organisms, whereas ultimate explanations are about populations. The question, "Why do beavers build dams?" may be answered in two different ways. In one interpretation, the account would refer to stimuli from water and trees, the structure of the nervous system, hormones, and so on. It would explain how the cluster of genes that make for dam building express themselves in physiology and interact with the environment to ensure that Beaver X, alive today, builds a dam. That would be a proximate explanation. The ultimate explanation, in contrast, would make no reference to Beaver X, but would be about beavers as a species or about a population of beavers or about the gene pool of a

population of beavers, to which Beaver X or its genes might belong. It would refer to the adaptive consequences of building dams, variation within populations long ago, and increase in the frequency of alleles promoting dam building. It would explain how those alleles became common in the gene pool. Proximate explanations are silent about where the mechanisms for dam building came from. Ultimate explanations are silent about Beaver X, except to say that Beaver X builds a dam because it is the nature of beavers to build dams, and then to explain where that nature came from. So to speak, ultimate explanations are about the forest, whereas proximate explanations are about the trees.

Proximate explanations explain the behavior of individual organisms in terms of present mechanisms, whereas ultimate explanations explain patterns of frequency within a pool, such as those shown in Fig. 24.1, in terms of a process of differential success. Proximate explanations refer to causes in the present, whereas ultimate explanations rely on processes that may be called historical, because they extend in time (Baum and Heath, 1992). Evolutionary change results from continual operation of the process of selection over a period of time. That it takes time may be incidental, because it is a process of adjustment with a beginning in a disturbance (in the environment or in the population) and an end in a stabilized population. It is understood as a whole; at any point in-between, it is incomplete. Suppose the shaded bars in the middle panel of Fig. 24.1 represent the relative rates of success (recurrence) from one time period (eg, generation) to the next. Although variant A is lowest in frequency, it has the highest rate of recurrence. Given this pattern, we expect the frequency of variant A to increase, and the frequencies of B, C, and D to decrease. If relative recurrence is independent of frequency, the process will be incomplete until A dominates. (If relative recurrence is frequency dependent, a different equilibrium results, but that in no way affects this discussion.) Suppose the curve in the lower panel of Fig. 24.1 shows relative recurrence for the continuous case. The situation is essentially the same; we expect the frequency distribution to shift to the right. Eventually, we expect its maximum to coincide with the maximum of the curve; then the distribution stabilizes, and selection acts to keep it stable.

Cultural Proximate and Ultimate Explanations

Since every evolutionary process includes the distinction between the mechanism that produces the advantageous behavior and the history of advantage for that behavior, cultural evolution and behavioral evolution also admit of the distinction between proximate and ultimate explanations (Alessi, 1992). In cultural evolution, the mechanism by which a custom is transmitted explains why it persists (ie, why it recurs), whereas the prevalence of the custom ultimately lies in a history of competition and selection. As with the question, "Why do beavers build dams?" the question, "Why does this tribe adorn themselves with tattoos?" may be interpreted and answered in two different ways. In the proximate interpretation, the question might be reworded as, "Why do the members of the Hell's Angels motorcycle club wear the club's tattoos?" Alternatively, "Why does Tom, who belongs to Hell's Angels, wear the tattoos?" Three or more mechanisms of transmission might be involved. Tom might imitate other members of the tribe. Other members might instruct Tom: "If you want to be accepted, you should get the tattoos." Once Tom began getting tattoos, reinforcement from tribe members might lead to getting more tattoos. In the ultimate interpretation, the question might be reworded as, "How did it come about that the Hell's Angels wear those tattoos?" The answer would refer to the history of selection in the culture pool. Tattooing may have competed with other forms of adornment, such as wearing black jackets, wearing hair in a ponytail, or speaking in a certain dialect. One or two members may have gotten tattoos. Other members who saw them frequently may have imitated them as a result. Boyd and Richerson (1985) call this *frequency-dependent bias*. The first members with tattoos may have been imitated by the other members or may have been able to instruct the other members because they held high status in the club. Boyd and Richerson (1985) call this tendency to imitate success *indirect bias*. Tattooing may have worked better to identify members because other groups might wear black jackets or ponytails and because dialects vary from region to region; tattoos are permanent and unambiguous. Boyd and Richerson (1985) would call reinforcement of a custom by such an environmental effect *direct bias*. Any combination of indirect bias, frequency-dependent bias, and direct bias would result in an increase in the frequency of wearing tattoos among the tribe, until the wearing of tattoos became virtually universal.

Nesting of Evolutionary Processes

Genetic evolution may be thought of as an overlay on cultural evolution. Ultimate and proximate genetic explanations may be constructed for the question, "Why do the Hell's Angels wear tattoos?" They would be analogous to the explanations of dam building in beavers. The proximate rewording of the question would be, "Why did Tom get himself tattooed?" As with Beaver X, the explanation refers to stimuli (eg, from the behavior of other members), reinforcers (eg, from the other members), development (eg, early exposure to Hell's Angels), and physiology (eg, brain mechanisms)—all of which might be traced to gene expression. The genetic ultimate explanation rewords the question as, "How is the wearing of tattoos beneficial to the

members of the tribe?" The answer might be that it constitutes symbolic marking of the group, distinguishing it and promoting cohesion within it, which in turn promotes group selection for various forms of cooperation, which enhance the success of the group and thus boost the members' reproductive success. It would include also the advantages to alleles that make for frequency-dependent bias, indirect bias, and direct bias in competition with alleles that do not (Boyd and Richerson, 1985; Richerson and Boyd, 2000). Other stories might be told, but they would all end with the same reference to reproductive success, because in a genetic ultimate explanation genes must be selected. The biasing effects of genes ensure that any custom that decreases reproductive success, even if common for a time, is likely to disappear eventually.

The General Evolutionary Process

Fig. 24.2A diagrams an evolutionary process in general terms and shows the different focuses of proximate and ultimate explanations. Each of the variables, *V*, *F*, *E*, or *R*, may be thought of either as a pool of variants, as a frequency distribution across variants, or as a frequency of a particular variant relative to all others. In the parlance of cybernetics, they are operands and transforms, whereas the rectangles represent processes (transformations) that produce transforms from operands (Ashby, 1956). A pool of variants (process) results in *V*, a distribution of substitutable variants or relative frequency of a particular variant relative to all its competitors. A process of expression transforms *V* into *F*, a distribution of interactors (or vehicles) or frequency of one type of interactor relative to all others. The expression process receives input from the environment, omitted from Fig. 24.2 in the interest of simplicity. The input is represented by levels of variable *N* (N_1—N_6) in Fig. 24.3, which illustrates the various transformations in Fig. 24.2A. The top line of Fig. 24.3 shows V_i composed of three variants, A, B, and C, having equal frequencies. The different levels of the environmental variable *N* affect the outcomes in F_i; so that B coupled with N_2 goes to α, the same outcome as A coupled with N_1, whereas B coupled with N_3 goes to β, and C transforms to β, γ, or δ, depending on *N*. In this illustration, the variation in *N* results in a distribution F_i that has more variety than V_i.

A set of external standards or contingencies, which might be characterized as a set of if-then rules, transforms *F* into *E*, a distribution of external effects. These are shown in Fig. 24.3 as levels of *W*, *X*, *Y*, and *Z*, just to emphasize that they are transforms of the elements of F_i: *W* goes with α, *X* with β, *Y* with γ, and *Z* with δ. They may be thought of as levels of success—eg, reinforcer rates or numbers of matings. *E* feeds back to a recurrence process, which results in R_i, a distribution of recurrence rates or a relative recurrence rate. Following the example in Fig. 24.3, if the elements of

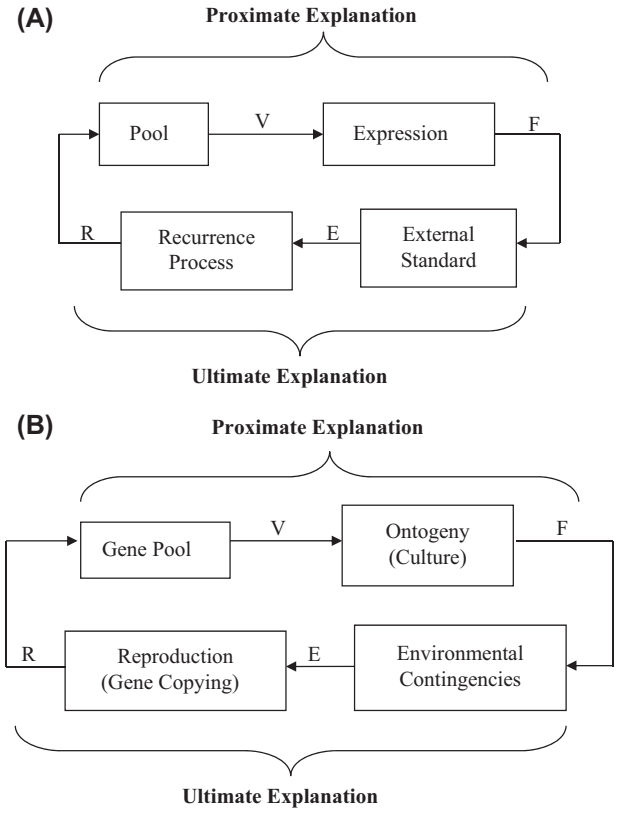

FIGURE 24.2 (A) The general evolutionary process as a flow chart. A distribution of substitutable variants, *V*, is transformed by expression into a distribution of interactors, *F*, which an external standard transforms into a distribution of effects, *E*, which recurrence transforms into a distribution of recurrences, *R*, which enters or replaces the pool to produce a new transform *V*. (B) The general evolutionary process chart applied to genetic evolution. A distribution of alleles (*V*) is transformed by ontogeny (eg, culture) into a distribution of phenotypes (*F*), which environmental contingencies transform into a distribution of environmental effects (*E*), which gene copying transforms into a distribution of recurrences (*R*), which updates the gene pool and produces a new distribution of alleles.

E associated with *A* (W_1—W_4) have a collective weight of 10 (6 + 3 + 1), those associated with B have a collective weight of 6, and those associated with C have a collective weight of 8 (entirely due to the fortunate occurrence of N_6, which resulted in transform δ in F_i), then the frequencies in R_i reflect these collective success rates. The appearance of variant D, however, has nothing to do with these success rates, but rather represents some kind of accident: a mutation, copying error, or external force. R_i closes the loop by entering the pooling process to result in the new distribution of variants V_{i+1}.

If this system is disturbed by a change in the pool (eg, mutation or immigration) or in the external standards (eg, a change in climate), resulting in disequilibrium like that depicted in Fig. 24.1, it will tend to move back toward equilibrium, because iterations of the feedback loop cause

Transformations in an Evolutionary Process

V_i:	A	A	A	A	B	B	B	B	C	C	C	C
N:	N_1	N_1	N_1	N_1	N_1	N_3	N_3	N_3	N_4	N_5	N_5	N_6
F_i:	α	α	α	α	α	β	β	β	β	γ	γ	δ
E_i:	W_1	W_2	W_3	W_4	W_5	X_1	X_2	X_3	X_4	Y_1	Y_2	Z_1
e.g.:	6	3	0	1	0	0	2	4	0	0	0	8
R_i:	A	A	A	A	A	B	B	B	C	C	C	D
V_{i+1}:	A	A	A	A	A	B	B	B	C	C	C	D

FIGURE 24.3 Illustration of the transformations of Fig. 24.2. In generation *i*, distribution *V* contains three substitutable variants, A, B, and C, with equal frequencies. The input *N* has six levels, N_1–N_6, which enter the transformation to *F*, a distribution of interactors that contains four different interactors, α, β, γ, and δ, in unequal frequencies. This is transformed to a distribution of effects, labeled *W*, *X*, *Y*, and *Z* to correspond with α, β, γ, and δ. In the example, the effects for A, W_1–W_4, sum to 10, the effects for B, W_5–X_3, sum to 6, and the effects for C, X_4–Z_1, sum to 8. These sums determine the frequencies in the distribution of recurrences *R*. A new variant (accident), D, also arises in *R*. In this example, the recurrence distribution for generation *i* becomes the distribution of substitutable variants for generation $i + 1$.

the composition of the pool to change until it comes into accord with the external standards—ie, to an optimal fit.

Fig. 24.2A also illuminates the roles of proximate and ultimate explanations (braces). The links from the pool to the external standards—ie, from *V* to *F*—constitute the focus of proximate explanations. They pose the question, "By what mechanisms does a distribution of variants result in a distribution of interactors?" The links from the external standards to the pool constitute the focus of ultimate explanations. They pose the question, "How does the distribution of external effects change the composition of the pool?" That is a question about selection. The diagram omits any explicit indication of the iterative nature of evolutionary change; that must be taken for granted. The reason that both proximate and ultimate explanations are necessary for a full understanding is that the two explanations address different parts of a whole process—mechanical connection and feedback, immediate causation, and history.

Genetic Evolutionary Process

Fig. 24.2B shows the general diagram applied to genetic evolution. The gene pool offers a distribution (*V*) of genotypes. Ontogeny or development transforms *V* into a distribution (*F*) of phenotypes. Environmental contingencies specify a distribution (*E*) of environmental effects, such as rates of obtaining resources, of predation, or of mating. Reproduction, which may be thought of as gene copying, depends on *E*. Sometimes it is thought of as simple transmission of genes from parents to offspring, but it may also be complex, because it may be the locus of other forms of selection besides natural selection—eg, sexual selection. Its outcome *R*, the distribution of copying rates (fitnesses), in turn changes or maintains the composition of the gene pool. Proximate explanations focus on processes of ontogeny and development. Ultimate explanations focus on the feedback, the way the environmental contingencies and reproduction achieve selection among genotypes.

As an example, we may apply Fig. 24.2B to the evolution of culture—that is, the transition from a noncultural species to a cultural species as a result of genetic evolution (as opposed to cultural evolution, our second process). Ontogeny converted the distribution of genotypes *V* into a distribution of phenotypes (*F*) that varied in ability and propensity for culture—that is, in the mechanisms that cause a group of people to have a culture (group-level behavior transmitted from member to member). Elsewhere I have argued that three mechanisms would suffice: sensory specializations, imitation, and social reinforcers (Baum, 2000, 2005). Whether or not these are the answer, they suggest the sort of mechanisms that would constitute a proximate explanation for the development of culture in children and newcomers to a group. The distribution *F* might be called "variations on culture." A highly variable environment made culture beneficial to the hominids that possessed even its rudiments (Boyd and Richerson, 1985; Richerson and Boyd, 2000). It would, for example, solve many problems related to the obtaining of resources and mates. Those variants favored in the distribution of environmental effects (*E*) would be more represented in distribution *R*, with the result that the genes underlying the mechanisms for culture would increase in the gene pool. That feedback would be the ultimate explanation for the existence of culture.

Nesting Cultural Evolution Within Genetic Evolution

Fig. 24.4 diagrams the relationship between genetic evolution and cultural evolution and the different focuses of their proximate and ultimate explanations. It shows two feedback loops: an outer loop symbolizing genetic evolution and an inner loop (enclosed in the box) symbolizing cultural evolution (cf. Burgos, 1997). The inner loop takes the place of ontogeny in Fig. 24.2B or expression in Fig. 24.2A. The culture pool may be thought of as all the

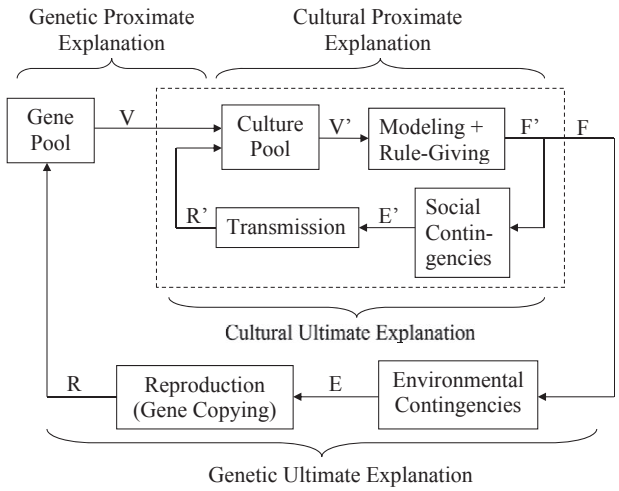

FIGURE 24.4 The cultural evolutionary process as an example of the general process (Fig. 24.2A) and as nested within the genetic evolutionary process. The rectangle of broken lines demarcates the cultural process. A distribution of all cultural variants (practices) available V' is transformed into a distribution of actually occurring variants F' by induction (eg, modeling) and rule-giving ("instruction"). The distribution F' comes into contact with social contingencies, which transform it into a distribution of social effects (reinforcement and punishment), E'. The distribution of effects is transformed by transmission into a distribution of recurrences of the practices R'. The distribution of genetic variants that interact with culture V enters the culture pool as input, thus affecting V'. The distribution of actually occurring practices F' corresponds also to the distribution F that is the operand for environmental contingencies that form the context for the cultural process. The braces indicate the focuses of the different proximate and ultimate explanations.

customs present in the group—the potential variants, resulting in a distribution V'. One might be tempted to think of V' as a distribution of memes. Our ignorance of the workings of the brain suggests that temptation is best resisted (Baum, 2000; Simon and Baum, 2011). The mechanism of expression, labeled "Modeling + Rule-Giving," embodies the vagaries of the social environment that transform V' into a distribution F' of actual cultural variants (customs). Models and rules are stimuli that may induce imitation and rule-following, behavior that may be reinforced or punished by group members (Baum, 2000). Alternatively, one might think of the culture pool as directly producing F'. (As before, F' could also represent the relative frequency of a particular custom.) The structure of the social environment, particularly social contingencies, results in a distribution E' of social consequences. For example, food sharing might result in approval, whereas food hoarding might result in disapproval or aggression. From E', transmission results in a distribution R' of recurrences that feeds back to change or maintain the composition of the culture pool. The means of transmission are imitation and instruction (Baum, 2000, 2005). They constitute the locus where Boyd and Richerson's (1985) indirect and frequency-dependent biases operate.

Fig. 24.4 depicts the way in which cultural evolution and genetic evolution may interact. The distribution F' interacts as F in the external loop (genetic evolution) with environmental contingencies to produce distribution E—that is, cultural practices may affect genetic evolution (Boyd and Richerson, 1985). If, for example, group members who shared food were more likely to marry, then any genes that promoted tendency to share food would be selected.

The braces in Fig. 24.4 indicate the different focuses of proximate and ultimate explanations in genetic and cultural evolution. Genetic proximate explanation focuses on the mechanisms by which genetic variants (distribution V; shown as input to the cultural pooling process) affect cultural evolution. Cultural proximate explanation focuses on the mechanisms (possibly in the nervous system, but specifically related to behavior in groups) by which cultural variants (distribution F') are expressed. Modeling and exhortation, for example, might induce food sharing. Cultural ultimate explanation focuses on the iterative feedback from social consequences that shapes the culture pool over time. Once induced, for example, food sharing might be reinforced by approval, status, or reciprocation. Genetic ultimate explanation focuses on the feedback from environmental consequences of culture on the composition of the gene pool. It represents the feedback of culture on genes that prompts Boyd and Richerson (1985) to speak of "gene-culture co-evolution." Failure to keep these four different types of explanation distinct is likely to result in confusion. For example, development (genetic proximate explanation) might account for the presence of imitation and instruction, which underlie cultural ultimate explanation of cultural change over time. Cosmides and Tooby's (1992) idea that cultural variation can be explained by genetic expression probably arises from confusing these two types of explanation.

Proximate and Ultimate Operant Explanations

In behavioral evolution (ie, shaping), the distinction between proximate and ultimate explanations is the distinction between physiological mechanism and history of reinforcement. Advantageous behavior is defined by reinforcement and punishment. Explaining the occurrence of advantageous behavior may refer to events in the nervous system or to the history of advantage. As with the other two evolutionary processes, a question like, "Why does Liz brush her teeth before she goes to bed?" has two interpretations. The proximate interpretation focuses on the mechanism: "On any particular night, what causes Liz's tooth brushing?" The proximate explanation would focus on stimuli that regularly precede going to bed and tooth brushing and events in the nervous system that result from

these stimuli and cause tooth brushing at that time. The ultimate interpretation focuses on a history of selection: "How did it come about that Liz brushes her teeth before bed?" or "What advantage has Liz derived for brushing her teeth?" The ultimate explanation focuses on the differential consequences of tooth brushing in Liz's life that selected tooth brushing at bedtime over other behavior that might have occurred at bedtime. It would refer to bedtimes in Liz's childhood, her father's exhortations, reprimands, and approval, and the later incorporation of tooth brushing into the pattern of behavior surrounding bedtime combined with events at the dentist's office. Different stories might be told, but they would all refer to the advantages of tooth brushing over time.

Nesting of Behavioral Evolution Within Cultural Evolution

Fig. 24.5 parallels Fig. 24.4, depicting the relationship between behavioral evolution and cultural evolution. The inner loop, behavioral evolution, contains the same elements as in Fig. 24.2A. It stands in the place of "Modeling + Rule-Giving" in Fig. 24.4 or "Expression" in Fig. 24.2A. The behavior pool consists of all the individual's potential behavior—species-specific behavior plus all the behavior ever expressed in this individual. It results in a distribution V'' of behavioral variants. The culture pool adds to the individual's behavior pool via the distribution V'. The mechanisms of stimulus control, including induction, transform V'' into a distribution (or relative frequency) F'' of presently occurring behavior. Those mechanisms correspond to what Staddon and Simmelhag (1971) called "principles of variation." The structure of the environment, in the form of contingencies of reinforcement and punishment (or reinforcement and punishment feedback functions; Baum, 1973, 1989, 2012), converts F'' into a distribution E'' of environmental effects, or consequences. These reinforcers and punishers constitute the relatively immediate tokens of ultimate reproductive success discussed earlier. Distributed differentially over behavioral variants, they result via mechanisms in the body, particularly in the nervous system, labeled "habit" in Fig. 24.5, in a distribution R'' of (relative) recurrences, which in turn changes or maintains the composition of the behavior pool. The behavioral proximate explanation focuses on the stimuli and physiological mechanisms that cause the behavior on particular occasions. The behavioral ultimate explanation refers to the selective effect that the token consequences have on the mechanism and behavior over time. A proximate explanation of sharing meat with other group members would point to the occasion of returning to one's village with a captured animal. The ultimate explanation would point to the history of exhortation in favor of sharing, social reinforcement for sharing, and punishment of hoarding. The effect of differential consequences on individuals' behavior provides the means for the cultural effects that Boyd and Richerson (1985) call guided variation and direct bias. Guided variation names the contribution of individual innovation to the culture pool. For example, the individual who makes a better arrowhead may catch more food personally, but the method also may be incorporated into the culture pool by imitation and instruction. As we have already seen, direct bias is the effect of the token consequences on transmission of practices. The method of making the better arrowhead personally benefits anyone who uses it. The effect of behavioral evolution on cultural evolution is symbolized by the output of distribution F'' as F' to cultural contingencies, which in turn produce E', the distribution of social consequences.

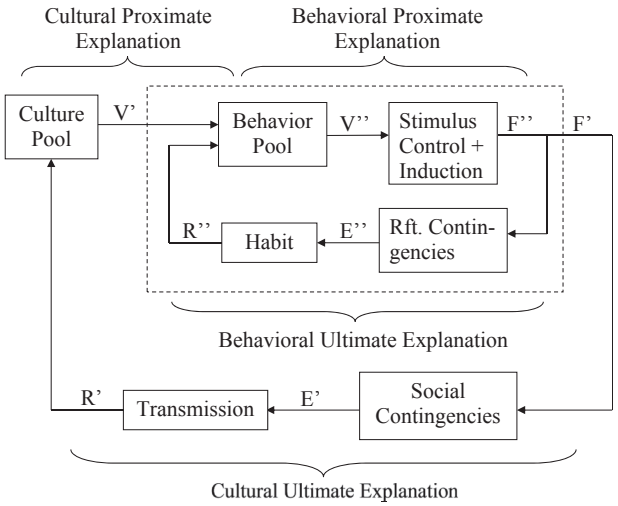

FIGURE 24.5 The operant (behavioral) evolutionary process as an example of the general process (Fig. 24.2A) and as nested within the cultural evolutionary process. The rectangle of broken lines demarcates the operant process. A distribution of all behavioral variants available V'' is transformed into a distribution of actually occurring variants F'' by stimulus control and induction (eg, by releasers). The distribution F'' comes into contact with reinforcement contingencies, which transform it into a distribution of effects (reinforcement and punishment), E''. The distribution of effects is transformed by habit (ie, physiological mechanisms) into a distribution of recurrences of the behavioral variants R''. The distribution of cultural variants that interact with individual behavior V' enters the behavior pool as input, thus affecting V''. The distribution of actually occurring behavior F'' corresponds also to the distribution F' that is the operand for social contingencies that form the context for the individual process. The braces indicate the focuses of the different proximate and ultimate explanations.

Taken together, Figs. 24.4 and 24.5 suggest two levels of nesting. Evolution of individual operant behavior is nested within cultural evolution, which is nested within genetic evolution. To understand human behavior, one needs to attend to all three levels and to all the various proximate and ultimate explanations they imply.

In a noncultural species, the behavioral inner loop is directly nested within the genetic outer loop (cf. Burgos, 1997). In that situation, gene expression affects the mechanism that causes the behavior and is sensitive to feedback from the token consequences. As in cultural evolution, the token consequences affect gene copying, which feeds back on the composition of the gene pool, favoring alleles that promote the mechanism that allows behavioral evolution in the first place. If we ask why a laboratory rat presses a lever in an operant chamber, the answer might begin with an explanation of why the rat is so constructed that a contingency between presses and food pellets affects its behavior—ie, the advantages of learning by reinforcement (Baum, 2005; Donahoe, 1999; Zeiler, 1999).

An Example: Self-Control

Behavior analysts have progressed on the problem of understanding self-control. Initially, it was analyzed as a conflict between deferred and immediate consequences (Ainslie, 1974). Self-control consists of choosing behavior that pays off in the long run over impulsiveness, which is behavior that pays off in the short run. For an alcoholic, acceptance of a drink is immediately reinforced, whereas abstinence, though it has a greater reward, is reinforced only at a great delay. The question remains, however, as to how the deferred consequences ever overcome the influence of the relatively immediate ones. How does self-control ever predominate? Rachlin and Green (1972) suggested one possibility: commitment. If one acts at an early time to prevent choosing impulsiveness (eg, having part of one's salary deposited directly to a savings account before one can spend it), then self-control becomes more likely when the choice arises. Most situations calling for self-control, however, offer no opportunity for commitment, because occasions for impulsiveness are frequent and unpredictable. Some alcoholics take drugs that produce noxious effects when alcohol is in the bloodstream, and some dieters have their jaws wired shut, but most people rely on other means.

Rachlin (1995) argued that self-control might be better understood if it were seen as a pattern of choices extended over time. Occasional impulsiveness ("defection" from the overall pattern) might occur without necessarily disrupting the extended pattern of "doing the right thing." The temporally extended pattern we call eating a healthy diet constitutes self-control even if it is peppered with minor defections like having an ice cream cone. The extended pattern, Rachlin argued, has a higher value—ie, produces greater reinforcement—than any defection. Those greater and temporally extended consequences explain the persistence of the pattern.

Rachlin's (1995) account stops, however, at an awkward place. Although it helps to frame the initial question, it leaves the question unanswered: how does the pattern of self-control ever emerge and persist in the face of frequent opportunities for gaining immediate reinforcement for impulsiveness? In comparison with the contingencies favoring impulsiveness—powerful because of the relative immediacy of the reinforcement—the contingencies favoring self-control are weak and vulnerable because of their temporal extendedness, as in our comparison to group selection. How could the weak selection ever prevail?

That question raises at least two others: (1) why would an individual care about eating a healthy diet in the first place?; and (2) why would such a concern spread and persist among many members of a society? On the surface, the answers might seem obvious: quality of life and longevity. Quality of life, however, is a social construct, requiring explanation itself, and death cannot punish nor can longevity reinforce any subsequent operant behavior. Instead, the two questions may be interpreted as being about cultural and genetic evolution: (1) why do other members of a group promote and enforce eating a healthy diet?; and (2) how are genes selected that support acquisition and maintenance of behavior like eating a healthy diet? The answer to the first question requires identifying self-interest on the part of one member in other members' health. Such is near at hand, because practices concerning medicine and public health in advanced societies today are costly for the entire group (taxpayers, at least). The contingencies involved may be compared to those involved in so-called "altruism." We sacrifice to benefit others if greater benefit accrues to us eventually. The sacrificial behavior is dangerous, however, because of the possibility of cheating—ie, someone's reaping benefits without paying the cost. When most members contribute to the cost of maintaining health in all, poor health is analogous to cheating. Customs promoting and enforcing health-enhancing behavior are selected in such a social setting (see "social contingencies" in Figs. 24.4 and 24.5). The whole extended pattern of healthy eating is selected, in analogy to group selection, as in Eq. (24.2).

A possible way that genes might be selected that support eating a healthy diet would be in response to variability in foods available from one environment to another. The advantages to imitation and easy instruction discussed earlier would apply to dietary habits. If you are an immigrant or child newly arrived in a group, the diet eaten by those around you is more likely to promote health than one you choose for yourself. Genes favoring imitation and easy instruction would be selected.

These suggested explanations are incomplete and may be incorrect, but they illustrate the sort of ultimate operant, cultural, and genetic explanations that an understanding of self-control requires. Many of the ideas are open to empirical study. They point to directions in research on behavior within an evolutionary framework.

CONCLUSION

Viewed from a sufficiently general perspective, such as diagrammed in Fig. 24.2A, genetic, cultural, and behavioral evolution all may be seen as examples of the same sort of evolutionary process. Since all three allow the distinction between immediate causation of behavior and the historical origin of the causes, all three allow both proximate and ultimate explanations. Indeed, full understanding requires both proximate and ultimate explanations. The nesting of the three processes in the way suggested in Figs. 24.4 and 24.5 means that the study of culture needs not only to take account of cultural evolution, but to be aware of the constraints imposed by genetic evolution and the contributions of operant behavior and its evolution to cultural evolution. Similarly, the study of human behavior needs to take account of the constraints imposed by both cultural evolution and genetic evolution. A complete explanation of a behavioral pattern needs to go beyond the processes that govern individual behavior. It needs to specify the provenance of behavior in cultural customs and in genetic effects on development and to explain the origins of effective stimuli and consequences in cultural and genetic evolution.

ACKNOWLEDGMENTS

I thank M. Ghiselin, S. Glenn, K. Panchnathan, P. Richerson, and H. Rachlin for helpful comments on an earlier draft.

REFERENCES

Ainslie, G.W., 1974. Impulse control in pigeons. Journal of Experimental Analysis of Behavior 21, 485–489.

Alcock, J., 1993. Animal Behavior, fifth ed. Sinauer Associates, Sunderland, MA.

Alessi, G., 1992. Models of proximate and ultimate causation in psychology. American Psychologist 47, 1359–1370.

Ashby, W.R., 1956. An Introduction to Cybernetics. Methuen, London.

Baum, W.M., 1973. The correlation-based law of effect. Journal of Experimental Analysis of Behavior 20, 137–153.

Baum, W.M., 1976. Time-based and count-based measurement of preference. Journal of Experimental Analysis of Behavior 26, 27–35.

Baum, W.M., 1989. Quantitative prediction and molar description of the environment. Behavior Analysis 12, 167–176.

Baum, W.M., 1995a. Introduction to molar behavior analysis. Mexican Journal of Behavior Analysis 21, 7–25.

Baum, W.M., 1995b. Rules, culture, and fitness. Behavior Analysis 18, 1–21.

Baum, W.M., 1997. The trouble with time. In: Hayes, L.J., Ghezzi, P.M. (Eds.), Investigations in Behavioral Epistemology. Context Press, Reno, NV, pp. 47–59.

Baum, W.M., 2000. Being concrete about culture and cultural evolution. In: Thompson, N., Tonneau, F. (Eds.), Perspectives in Ethology, vol. 13. Kluwer Academic/Plenum, New York, pp. 181–212.

Baum, W.M., 2001. Two stumbling blocks to a general account of selection: replication and information. Behavioral and Brain Sciences 24, 528.

Baum, W.M., 2002. From molecular to molar: a paradigm shift in behavior analysis. Journal of Experimental Analysis of Behavior 78, 95–116.

Baum, W.M., 2004. Molar and molecular views of choice. Behavioural Processes 66, 349–359.

Baum, W.M., 2005. Understanding Behaviorism: Behavior, Culture, and Evolution, second ed. Blackwell, Malden, MA.

Baum, W.M., 2012. Rethinking reinforcement: allocation, induction, and contingency. Journal of Experimental Analysis of Behavior 97, 101–124.

Baum, W.M., 2013. What counts as behavior: the molar multiscale view. The Behavior Analyst 36, 283–293.

Baum, W.M., 2016. Driven by consequences: the multiscale molar view of choice. Managerial and Decision Economics (in press).

Baum, W.M., Davison, M., 2004. Choice in a variable environment: visit patterns in the dynamics of choice. Journal of Experimental Analysis of Behavior 81, 85–127.

Baum, W.M., Heath, J.L., 1992. Behavioral explanations and intentional explanations in psychology. American Psychologist 47, 1312–1317.

Baum, W.M., Rachlin, H.C., 1969. Choice as time allocation. Journal of Experimental Analysis of Behavior 12, 861–874.

Benedict, R., 1934. Patterns of Culture. New American Library, New York.

Boyd, R., Richerson, P.J., 1985. Culture and the Evolutionary Process. University of Chicago Press, Chicago.

Boyd, R., Richerson, P.J., 1992. Punishment allows the evolution of cooperation (or anything else) in sizable groups. Ethology and Sociobiology 13, 171–195.

Burgos, J.E., 1997. Evolving artificial neural networks in Pavlovian environments. In: Donahoe, J.W., Dorsel, V.P. (Eds.), Neural-Networks Models of Cognition. Elsevier Science, New York, pp. 58–79.

Campbell, D.T., 1965. Variation and selective retention in socio-cultural evolution. In: Barringer, H.R., Blanksten, G.I., Mack, R.W. (Eds.), Social Change in Developing Areas: A Reinterpretation of Evolutionary Theory. Schenkman, Cambridge, MA, pp. 19–49.

Cosmides, L., Tooby, J., 1992. Cognitive adaptations for social exchange. In: Barkow, J.H., Cosmides, L., Tooby, J. (Eds.), The Adapted Mind: Evolutionary Psychology and the Generation of Culture. Oxford University Press, New York, pp. 163–228.

Dawkins, R., 1989a. The Extended Phenotype: The Long Reach of the Gene. Oxford University Press, Oxford.

Dawkins, R., 1989b. The Selfish Gene, new ed. Oxford University Press, Oxford.

Diamond, J.M., 1992. Diabetes running wild. Nature 357, 362–363.

Donahoe, J.W., 1999. Edward L. Thorndike: the selectionist connectionist. Journal of Experimental Analysis of Behavior 72, 451–454.

El Mouden, C., André, J.–B., Morin, O., Nettle, D., 2014. Cultural transmission and the evolution of human behaviour: a general approach based on the Price equation. Journal of Evolutionary Biology 27, 231–241.

Ghiselin, M.T., 1997. Metaphysics and the Origin of Species. State University of New York Press, Albany, NY.

Gilbert, R.M., 1970. Psychology and biology. Canadian Psychologist 11, 221–238.

Glenn, S.S., Ellis, J., Greenspoon, J., 1992. On the revolutionary nature of the operant as a unit of behavioral selection. American Psychologist 47, 1329–1336.

Guerin, B., 1997. How things get done: socially, non-socially; with words, without words. In: Hayes, L.J., Ghezzi, P.M. (Eds.), Investigations in Behavioral Epistemology. Context Press, Reno, NV, pp. 219–235.

Henrich, J., 2004. Cultural group selection, coevolutionary processes and large-scale cooperation. Journal of Economic Behavior and Organization 53, 3–35.

Hull, D.L., 1988. Science as a Process: An Evolutionary Account of the Social and Conceptual Development of Science. University of Chicago Press, Chicago.

Hull, D.L., Langman, R.E., Glenn, S.S., 2001. A general account of selection: biology, immunology, and behavior. Behavioral and Brain Sciences 24, 511–573.

Mayr, E., 1959. Darwin and the evolutionary theory in biology. In: Meggers, B.J. (Ed.), Evolution and Anthropology: A Centennial Appraisal. Anthropological Society of Washington, Washington, D. C, pp. 1–10.

Mayr, E., 1961. Cause and effect in biology. Science 134, 1501–1506.

Mayr, E., 1970. Populations, Species, and Evolution. Harvard University Press, Cambridge, MA.

McElreath, R., Boyd, R., 2007. Mathematical Models of Social Evolution: A Guide for the Perplexed. University of Chicago Press, Chicago.

Price, G.R., 1970. Selection and covariance. Nature 227, 520–521.

Price, G.R., 1972. Extension of covariance selection mathematics. Annals of Human Genetics 35, 485–490.

Rachlin, H., 1994. Behavior and Mind: The Roots of Modern Psychology. Oxford University Press, New York.

Rachlin, H., 1995. Self-control: beyond commitment. Behavioral and Brain Sciences 18, 109–159.

Rachlin, H., 2002. Altruism and selfishness. Behavioral and Brain Sciences 25, 239–296.

Rachlin, H., Green, L., 1972. Commitment, choice, and self-control. Journal of Experimental Analysis of Behavior 17, 15–22.

Richerson, P.J., Boyd, R., 2000. Built for speed: Pleistocene climate variation and the origin of human culture. In: Thompson, N., Tonneau, F. (Eds.), Perspectives in Ethology, vol. 13. Kluwer Academic/Plenum, New York, pp. 1–45.

Richerson, P.J., Baldini, R., Bell, A., Demps, K., Frost, K., Hillis, V., Mathew, S., Narr, N., Newson, L., Newton, E., Ross, C., Smaldino, P., Waring, T., Zefferman, M.R., 2016. Behavioral and Brain Sciences 39.

Ringen, J., 1999. Radical behaviorism: B.F. Skinner's philosophy of science. In: O'Donohue, W., Kitchener, R. (Eds.), Handbook of Behaviorism. Academic Press, New York, pp. 160–178.

Seeley, T.D., 1989. The honey bee colony as a superorganism. American Scientist 77, 546–553.

Simon, C., Baum, W.M., 2011. Expelling the meme-ghost from the machine: an evolutionary explanation for the spread of cultural practices. Behavior and Philosophy 39/40, 127–144.

Simon, H.A., 1990. A mechanism for social selection and successful altruism. Science 250, 1665–1668.

Skinner, B.F., 1938. Behavior of Organisms. Appleton-Century-Crofts, New York.

Skinner, B.F., 1953. Science and Human Behavior. Macmillan, New York.

Skinner, B.F., 1957. Verbal Behavior. Appleton-Century-Crofts, New York.

Skinner, B.F., 1969. The phylogeny and ontogeny of behavior. In: Contingencies of Reinforcement: A Theoretical Analysis. Appleton-Century-Crofts, New York, pp. 172–217.

Skinner, B.F., 1981. Selection by consequences. Science 213, 501–504.

Staddon, J.E.R., 1973. On the notion of cause, with applications to behaviorism. Behaviorism 1 (2), 25–63.

Staddon, J.E.R., Simmelhag, V., 1971. The "superstition" experiment: a re-examination of its implications for the principles of adaptive behavior. Psychological Review 78, 3–43.

Tooby, J., Cosmides, L., 1992. The psychological foundations of culture. In: Barkow, J.H., Cosmides, L., Tooby, J. (Eds.), The Adapted Mind: Evolutionary Psychology and the Generation of Culture. Oxford University Press, Oxford, pp. 19–136.

Wilson, D.S., 1999. Evolutionary psychology: the new science of the mind, by David M. Buss. Evolution and Human Behavior 20, 279–287.

Zeiler, M.D., 1999. An odyssey through learning and evolution. Mexican Journal of Behavior Analysis 25, 259–272.

Chapter 25

A Psychoanalyst Views the Self Across Civilizations

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PROLOGUE

As important as it is to delineate the profound differences in the self across civilizations, it is also of considerable value to describe the journey a third generation, Jewish-American psychoanalyst had to undertake to understand the psychology of persons from different civilizations. There is much to learn from both. My interest in Asian cultures stemmed from my time at Antioch College in the early 1950s after I was already involved in Indian philosophy. Since all freshmen and transfer students were required to write a Life Aims Paper, I wrote rather grandiosely that I wanted to make an East–West comparison in a number of areas, such as philosophy, religion, literature, art, anthropology, sociology, and such. Over 25 years later, when I received an American Institute of Indian Studies grant to do clinical psychoanalytic research in India, having completely forgotten my Life Aims Paper, I found that was exactly what I had to do to begin to understand the Indian and then the Japanese psyche as a psychoanalyst. It is something that psychoanalysts and psychologists very rarely do.

My psychoanalytic journey actually started in New York City, when one evening in February in the early 1970s, after teaching a class on Identity, Identification, and Self-Image at The New School, a gaunt looking, intense Indian man, Ashis, in his early 40s, a graduate student in the arts at Columbia University, accosted me. He noticed from the catalog that I had already been to India, and he asked if I could see him in therapy since he felt his identity was deeply fragmented. From the first session on, I was struck by his enthusiasm and lack of ambivalence or doubt on beginning therapy, rather unusual for a man who had never been in therapy. I soon learned that in December his wife and mother had gone to the Brighu Temple in the Punjab, bringing the exact minute of his birth with them. A priest brought out a palm leaf manuscript written over 350 years ago that predicted in February (when he started therapy) he would embark on a new course that would help him significantly. I later encountered a similar prediction written over 1500 years ago with another Indian patient. In sessions, his mind worked in a very different way from any of my Euro-American patients, for which my study of Indian culture in college had not prepared me. He would frequently associate to three major Indian figures, Mahatma Gandhi, Rabindranath Tagore, and Ananda Coomeraswami, each standing for a different form of yoga, which he was trying to follow: Gandhi for *karma* yoga, Tagore for *bhakti* yoga, and Coomeraswami for *jnana* yoga. He further connected his somatic symptoms to his emotional distress, which I thought was from awareness of psychosomatic medicine. Instead, I found that in Hindu thought the mind and body are seen as being on a continuum rather than as a duality as in Western thought.

I soon learned of the enormous impact British colonialism had on his self through his father having a major post in the Indian Civil Service, where everything Indian was denigrated and all things British were idealized; then I learned of his sudden U-turn in early adulthood to a Hindu way through the teachings of the *Arya Samaj*. Suddenly, after two months of therapy, he decided to terminate just after having a dream with associations that revealed that his father committed suicide after being involved in a scandal. All of this was puzzling until I saw him several years later in Bombay for a longer period of therapy. I learned that his father had closely identified with the British and treated those under him in a stern, British hierarchical way. At the

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00025-9

time of Indian Independence in the late 1940s, his underlings brought him up on minor charges because they were highly irritated with his not treating them in the more Indian style of a nurturing hierarchical relationship. He was arrested and then committed suicide. I further learned the central importance to Indians of the family, and particularly of family reputation, which serves as an important self-object for self-esteem in Indians. Even his closest friends did not know of his father's suicide.

Before seeing Ashis, my wife and I had been to India in 1964 and had then decided to return for a year's research. In 1977, on the basis of my work with Ashis, I applied for and received an American Institute of Indian Studies grant for clinical psychoanalytic research on the effects of colonialism, Westernization, and modernization on urban educated Indians. In effect, it was to see the psychological effects of social change, something usually ignored across the board both in psychoanalysis and psychology with but a few rare exceptions. Then, I was to appraise differences in the Indian self from the self of my New York City Euro-American patients, and to see to what extent psychoanalytic theory needs to be amended. My wife received a Fulbright grant as a historian to study the Indian Jews of Bombay. I later decided to do similar psychoanalytic research in Japan, as I found that the only psychological comparisons were between India and the West (Kakar, 1978) and Japan and the West (Doi, 1973), and none on inter-Asian psychological comparisons.

In the fall of 1978, after returning to New York City from India, I presented a paper at the International Psychoanalytic Association's annual conference, "The Familial Self, the Individualized Self, and the Spiritual Self: Psychoanalytic Reflections on India." The Chair of the Panel was Dr. Nishizono, an important psychoanalyst in Kyushu, Japan. He asked to have lunch with me before the panel because he saw many similarities between the Indian and Japanese familial self. This spurred me to go to Japan, which I did the summer of 1982 with a psychoanalytic group in Hiroshima run by Dr. Mikihachiro Tatara.

When I returned home to New York City in the late 1970s and early 1980s from India and Japan, it was evident that my understanding of the Indian and Japanese psyches necessitated a deep knowledge of their culture, social relationships, and child-rearing. I therefore thought it wise to begin delving into the culture of modern Western individualism, not only for a greater understanding of my Euro-American patients but equally so for a reevaluation of psychoanalytic theory and therapy, and also for a better understanding of Indian and other Asian Americans who develop a bicultural self. It was much the same road that the French anthropologist Louis Dumont traveled on: first doing an anthropological study of Indian hierarchical relationships in 1970, then delving into the modern Western culture of individualism in 1986. His latter book became enormously helpful to me. I began to see that psychoanalysis has been in a dialectical dialog with the Western culture of individualism: gradually critiquing its rationality and basic assumption of the self-contained individual, while unreflectingly assuming some of its core values, such as the values of independence and autonomy, authenticity, the self-creation of one's identity, firm outer ego boundaries, self-reliance, a consistent superego, and predominant verbal communication, among others.

Clinically, I began to investigate and reflect on the sociocultural backgrounds of all of my American patients, and I became much more sensitive to how it affects their psyches (Roland, 1996). Indeed, we all come from a particular sociocultural background with its predominant kinds of cultural values and assumptions, social relationships, and child-rearing. It has made me far more sensitive to these issues of diversity in what is usually thought of as a relatively non-diverse population than I used to be, and more so than many other psychoanalytic therapists. Over a period of more than 35 years from frequent visits to India and Japan, and working with Asian and Asian-American patients (Indians, Japanese, South Koreans, Chinese, and Vietnamese) in New York City, I wrote three books (Roland, 1988, 1996, and 2011), as well as numerous articles, chapters for other books, and such.

THE SOCIAL AND CULTURAL CONTEXTS OF THE FAMILIAL SELF

Once I arrived in India in 1977 to do my clinical psychoanalytic research, I found that empathy was insufficient to understand the Indian self. I learned often to use patients to ascertain what was usual and normal or skewed in their relationships, as it appeared that the normality–psychopathology continuum was different. I also learned a great deal from other psychoanalytic therapists to help me understand puzzling scenarios, as well as from child development and cultural psychologists, from psychiatrists, anthropologists, literary persons, philosophers, and such. Without them I would have been clueless and would have begun to view the Indian self through a Western, colonial lens, as has so often happened.

An example of a most helpful informant was Professor Anandalakshmi, at that time director of the postgraduate program in child development at Lady Irwin College in New Delhi. She was the foremost child development psychologist in India, who was trained in the United States but upon returning to India realized that Indian child-rearing and development are significantly different from what she had learned in America. This was unique as Indian psychology tended to follow either the American or British models. Almost a decade before Takeo Doi's important book, *Anatomy of Self* (1986), detailing the Japanese dual self structure, she told me about the Indian dual self

structure where the social presentation of self meets the expected social etiquette of the formal hierarchical relationships, while a highly private self keeps all kinds of feelings, fantasies, and thoughts to oneself, only revealing them to someone who is experienced as being receptive. Authenticity in social relationships is not particularly valued as it tends to be in Western countries. Further, because Indians have a much more permeable outer ego boundary between self and others in their hierarchical intimacy relationships, the private self with its strong inner ego boundary protects them from feeling engulfed.

Doi (1986) commented that a balance must be kept between the two selves. If persons go too much by their social self in meeting the social etiquette of hierarchical relationships, they may become out of touch with their private self. On the other hand, if persons are unduly oriented toward implementing their private self, they soon create considerable disturbance in the hierarchical relationships.

I soon came upon this dual self structure in my clinical work. I began working with an Indian woman psychologist, Shakuntala, who with the other psychologists and social workers in their psychoanalytically oriented mental health clinic were required to be in psychoanalytic therapy. She had been in twice-a-week psychoanalytic therapy with a Bombay therapist who then left for further training in England shortly before I arrived. In a year and a half of twice-a-week therapy, she apparently had never voiced her two most salient, preoccupying conflicts: whether to continue an affair with a married man versus having an arranged marriage that her mother was pressuring her to have; and whether or not to leave Bombay, the affair, and her work to go to her aunt's ashram in Hardwar to become a guru, as her aunt, a well-regarded guru there, thought she was capable of becoming one. She felt her former therapist would not be receptive to either conflict. I do not know of any American patient I have worked with who could keep these preoccupying thoughts and emotions totally private for well over a year's time. They would either voice them or leave.

Another example was working with one of the social workers at the Indian Council of Mental Hygiene in psychoanalytic therapy, and observing her at a work situation at an elementary school. There, she was exceedingly gracious and compliant with her superior but in session excoriated him for the way he conducted himself. Then, another telling situation was with our 5½-year-old son, who after a month in Bombay began having nightmares. He gradually moved the fort he had been building with blocks in the middle of his bedroom to the corner of his room, as if his back was up against the wall. That he had enormous anxiety was evident, but we had no idea what it stemmed from. It was only when we took a two-day vacation away from our *ayah* (maid or nanny), Natalie, that our children revealed that Natalie was constantly hugging him, as were the teenage girls across the hall from us. It was only after I told both Natalie and the girls in as tactful a way as I could muster not to touch him, that American children were not used to being hugged all of the time, that his nightmares went away. An Indian psychoanalyst explained to me that an Indian child would have a much more private self with much firmer inner ego boundaries, so that he would not feel engulfed by the normal constant hugging as our son apparently was.

Another instance of gaining a major insight into the Japanese and Indian selves that I could not have arrived at by myself came from Dr. Moses Burg in Tokyo. He is an American psychoanalytic therapist who had a high level position in the occupation of Japan in the 1940s, married a Japanese woman, and stayed on. He pointed out that in Japanese insider relationships, the dependency, and asking of another, what Doi (1973) highlights as *amae* and *amaeru*, is actually a form of giving. It establishes the other as a hierarchical superior, whose esteem is considerably enhanced by being able to give. I later confirmed that this is equally present in Indians in a conversation with Dr. B.K. Ramanujam. However, it is totally at odds with American style relationships.

An example of this was cited in a case by a Japanese woman in training in psychoanalytic therapy. An adopted son of a wealthy business man grew up and had a difficult relationship with his father, whom he felt did not treat him well. Unlike his sisters who asked the father for new cars, refrigerators, and such, he refused to ask his father for anything. This was an angry way to get even with his father whose esteem could not be enhanced by his gift giving.

Still another instance when I was thoroughly perplexed and needed assistance was going with one or another social worker or psychologist to counseling sessions with groups of 17- to 18-year-old college girls. I found that sooner or later in these sessions, one or another girl would talk about using Ouija boards to contact the spirit world. I asked an accompanying psychologist what this was all about. She explained that in a couple of years these girls would have an arranged marriage with no say about whom they would be married to and what family they would be married into. They, therefore, wanted to know what is in store for them in their future marriage. In no way was there a denial of the presence of the spirit world by the psychologist, also later confirmed by one of the Bombay psychoanalysts, only a psychological explanation of the college girls' motivation in contacting the spirit world. A caveat was added that too much contact with the spirit world could bring about undesirable effects on one's life.

In still another scenario, I told Anandalakshmi of our puzzling experience in a Chinese restaurant at Kemps Corner in Bombay. While our 5½-year-old son and 7-year-old daughter became restless toward the end of the meal and began to explore the restaurant, I noticed that young children in two Indian families were sitting very quietly and well

behaved throughout the entire meal until the family left. She replied that if the Indian children misbehaved, the parents and/or grandparents would have said to them, "What will auntie or uncle over there think of us?" Preserving family reputation is paramount.

To understand the familial self, it is first important to take into account four major sociocultural dimensions: (1) the three psychosocial dimensions of hierarchical relationships; (2) insider/outsider relationships; (3) family structure and relationships; and (4) child-rearing. I learned a great deal about these from reading the work of anthropologists, and also from the astute comments of Dr. B.K. Ramanujam in India and Dr. Tatara in Japan. The former came from a traditional Brahmin joint family, but then after becoming a doctor, he trained in psychoanalytic psychiatry at the Menninger Foundation in the United States, and then at Moseley Hospital in London, becoming the clinical director of the then leading psychoanalytic clinic in India, the B.M. Institute for Mental Health in Ahmedabad. Dr. Tatara was trained in the William Alanson White Institute in New York City and was later an Erikson Scholar at Austen Riggs in Stockbridge, Massachusetts.

The first psychosocial dimension of hierarchical relationships is the formal hierarchy, a reciprocal relationship based on age and gender, something anthropologists have studied at length. The subordinate is expected to be deferent and respectful to the superior, obedient, to look for guidance, and to fulfill expectations. In return, the superior is expected to be responsible and nurturing, and to convey expectations and guidance. Each supports the esteem of the other, a central psychological value both in India and Japan, as well as in other Asian countries, the subordinate through being nurtured by the superior; the latter through fulfilling his or her role as the nurturing superior gains considerable esteem. These expectations of subordinate and superior are obviously sometimes not met; when they are not, there can be considerable anger. In Hindu India, the expectations are very much tied into *dharma*, the highly contextual ethic that governs all roles in Indian life. In Japan, the expectations are very much related to Confucian contextual norms for the different life roles.

My distinct impression with the Japanese is that the social etiquette of their hierarchical relationships is more rigorous than in India, and must be more carefully observed. While Indians may verbally assent to the expectations of the superior, if they do not want to do it, they will not. Whereas Japanese, once agreeing to something the superior wants, feel absolutely obligated to do it no matter how angry it makes them feel. As one patient put it, "It can't be helped." The rigorousness of the social etiquette of Japanese formal hierarchical relationships is in part expressed through language. The respect language, which very few foreigners have mastered, has different words for the same object according to the nature of the hierarchical relationship. It is so complex that Japanese who are abroad for several years have difficulty mastering it upon returning home. Thus, for most Japanese, one is either in Japanese society or out of it. It is difficult going back and forth, which is not at all true of Indians.

It is clear that this kind of hierarchical relationship is very different from the Western one of contractual relationships with its rights and obligations. Both Indians and other East Asians in the United States have conveyed to me their hurt and level of upset by the usual forthright criticism and lack of nurturance from American superiors, both at work and in the university. In another instance, I was struck in session by the response of an Indian woman doctor in a residency who was grossly overworked, far more than her contractual agreement called for. While I felt anger at the chair of her department for his abrogating the contractual agreement, she kept repeating, "He doesn't respect me. He doesn't respect me."

Westerners can sometimes be totally unaware of the importance of formal hierarchical relationships and the stability they provide. When I returned to India in 1991 after 11 years, I was shocked to find the Bombay Psychoanalytic Society in disarray after being dynamic and growing in the late 1970s. I did a thorough inquiry and found the following causes. A highly respected English psychoanalyst, an important member of the International Psychoanalytic Association (IPA), who had been to Bombay a few times to give seminars and supervision, decided she would improve the Bombay Psychoanalytic Society by bringing in Western values. She believed that competency should be the key to important training positions within the Society rather than formal hierarchical relationships by seniority. She first arranged through the IPA that for a Bombay trainee to become a full-fledged psychoanalyst, he or she did not have to obtain the approval of the Calcutta Psychoanalytic Society, as had been the case for decades. This removed one layer of formal hierarchical relationships.

Then, she decided that the training analysts should only be the most competent ones, thereby demoting some senior members and elevating a few junior members to that position. This led to two untoward results: (1) the senior members who were demoted tended to withdraw from the society; and (2) this led to a junior member, with the assistance of a couple of junior colleagues, forcing out of the society a much more capable junior member, and then taking over the society and preventing any new trainees for a number of years. He was able to do this because the senior membership had been severely decimated by the English psychoanalyst.

I had noticed this same kind of occurrence in a man in his early 40s who came to me for therapy in Bombay in the 1990s with a debilitating depression. He was the oldest son in a business family with a good ongoing business his father had run. The father had sent him to an elite boarding

school, then to England for an engineering degree, and arranged a marriage for him with a woman from a well-to-do, highly cultured family. None of this could the father afford to do for the two younger brothers and sister. When he came back from England, he helped the family firm develop significantly, making much more money for everyone. However, when his father became seriously ill and incapacitated, the younger brothers out of envy rose up and forced him out of the business, nor would they compensate him with even a rupee, even though he had been an equal partner and a leader in the business. His mother sided with the younger brothers. He then went to his mother's house and there went on a hunger strike to death unless he was fairly compensated. Only then, after several days of his hunger strike were efforts made to give him his due, although I learned a couple of years later that they only gave him partial restitution. Thus, once the senior member, the father became ill and incapacitated, the younger brothers took over and forced him out, which resulted in the business significantly declining. Similar to the Bombay Psychoanalytic Society, it was only with the presence of the senior hierarchy, the father, did the fissures and rivalry between the brothers remain under control.

The second psychosocial dimension of hierarchical relationships is hierarchical intimacy relationships. While it is present among men, it is stronger among women (personal communication, Nandita Chaudhari). In this intimacy relationship, there is considerable warmth and closeness, a great deal of empathic nonverbal communication, outer ego boundaries that are quite permeable, and a strong wishing, wanting self. This can sometimes be observed over time of young women who marry and live in her husband's family. There, the relationship with her mother-in-law often starts out as a formal hierarchical relationship, sometimes quite stressful for the daughter-in-law. But once she has a baby, she and the mother-in-law often become much closer. While the relationship still has elements of a formal hierarchy, the hierarchical intimacy relationship can often predominate.

I had one woman patient in Bombay who lived in her in-laws' house by prior agreement to getting married, and she frequently bitterly complained that her mother-in-law was very difficult and not at all understanding of her professional duties. Eleven years later, I returned to Bombay and found that she and her husband had been encouraged to move to a separate apartment for certain financial reasons. She was then very upset that her mother-in-law would not visit and stay overnight to be with her and her grandchildren. We worked on a psychological understanding of her mother-in-law's early trauma of her mother dying when she was only 4 years old, and then how to deal with her so that she would visit and stay over.

In both India and Japan, one must take into account both the formal hierarchy and hierarchical intimacy relationships. All relationships are a combination in one way or another of both. I was told that the bowing in Japan, how many and how deeply the bow, is a combination of where one is at in the formal hierarchical relationship with the other, and the degree of intimacy one has with the other. If one is out of the country for too long, it apparently becomes difficult to assess this.

The third psychosocial dimension is hierarchy by the qualities of the person. In a silent way, Indians, Japanese, and other Asians gauge the personal qualities of others, whether or not the person has superior qualities. A person with such qualities may or may not be the superior in the formal hierarchy. It could well be a younger brother, a wife, a sister, or even a servant. While the superior in the formal hierarchy is deferred to and respected, the person with superior qualities tends to be venerated. One wants to be as close as possible to this person to absorb their qualities. This can also lead to a younger man in an organization or family with superior qualities being given greater responsibilities than others higher in the formal hierarchy, while simultaneously, the younger member relates in a respectful and deferent way to those superiors. I have seen this happen in the late 1970s in the Bombay Psychoanalytic Society when a younger, gifted member was given much greater responsibilities than usual and a leadership role, while still relating appropriately to his superiors.

When I was in Bangalore in 1980, I was invited to attend a meeting with Dr. Murthy who was visiting, a former Chair of the Psychology Department at the National Institute of Mental Health and Neuro Sciences (NIMHANS), currently living in the Aurobindo Ashram in Pondicherry. The meeting was held in the relatively small offices of the Psychology Department. When he appeared, suddenly all of the doors opened in the Psychology Department, and every psychologist as well as many others came to attend, unlike other meetings I had been to. Many sat on the floor literally at his feet. It was clear he was a revered spiritual person, and everyone wanted to be as close as possible to share in his presence.

The second major dimension that must be taken into account is insider/outsider relationships, something again that Takeo Doi (1986) has written about with regard to the Japanese. Insider relations refer in India primarily to the family, to a certain extent to the community, and to close friends. It is one's own people and others. Hierarchical intimacy relationships are primarily related to the insider relationships of the family in India and Japan. Outsider relationships in India are generally not to be trusted unless someone you know well has a relationship with that person or business. There is also a tendency to take advantage of those in outsider relationships. On the other hand, if one develops a good relationship to an outsider in India, the strong tendency is to bring them home to the extended family so that they become an insider. One can then express

all kinds of wishes and desires to be fulfilled by the newly minted insider. I experienced this with my Bombay patients who sooner or later would invite me home to have tea or a meal with them, thus having me become an insider as part of the family.

I have also found the difference in insider/outsider relationships between Indians and Japanese in personal relationships. With Indians, if you are on more or less the same wave length, I have found one can make a close connection within a half hour. With Japanese on the other hand, I have found it takes several visits to establish the relationships and become more of an insider. An American physicist who had a fellowship to do research in a lab in Japan found that they would not even tell him where the test tubes were until a relationship was established, which took some time.

When I returned to New York City in the late 1970s, I was struck by the overwhelming reactions of my Euro-American friends and colleagues that they felt much more positively toward those from East Asian countries such as Japan or China, than to Indians. I spent a long time trying to figure this out, and I finally came to the conclusion that it had a lot to do with the differences in their insider and outsider relationships. Indians, as I have mentioned, try to convert any significant outsider relationship to an insider one. They often do this by asking for a lot, on the assumption that the other will have a significant increase in their self-esteem by fulfilling the dependency wishes of the former in an unstated hierarchical relationship. This mode of relating is totally foreign to Euro-Americans, and it is experienced as infringing on their autonomy. Japanese and other East Asians, on the other hand, with a Confucian ethic, keep outsider relationships as outsider relationships for a very long time. Whatever they may ask for in an outsider relationship is experienced as an obligation to reciprocate sooner or later; although in their insider relationships they function very similarly as Indians. Thus, it is very easy to visit an Indian family but extremely difficult to be invited into a Japanese family. Che Nakane (1970), a Japanese anthropologist who worked in India, has written at length about this. Since Japanese and other East Asians keep a much greater distance than Indians in their outsider relationships, Euro-Americans are more welcoming to them.

An example of this is an Indian student who asked my wife if he could take the final exam a few days earlier as his family was returning on a visit to India before finals. My wife agreed. The next day he returned to her saying that he approached his two other professors for the same request but they refused. Could my wife please persuade them to give him the final earlier. Most other professors would be incensed being asked to do this. But my wife had realized that by agreeing to give him the final earlier, she had become an insider familial figure, and therefore could be asked for anything. She, of course, politely refused his request.

In India, the family is the psychological and emotional center of life, which also includes men. With exceptions, of course, the work place does not have the same gravity and pull that it has in Japan, or even in the United States. Efforts have been made by consultants to have organizations incorporate some of the same modes of caring and relating that are present in the family to make it a more satisfactory place.

Even when the family is living as a unitary one with father, mother, and children, it is nevertheless an extended family. Important decisions by the elders of the family, even from another town or village, may shape the direction of the unitary family. Cousins are referred to as cousin brothers and cousin sisters, and relatives are free to visit and stay over. In a very traditional community, the children will only have relationships and play with those from their community. Further, the family has ties to other families, both of distant relatives and others, in their community or subcaste, which is the source of marriage partners either in a traditionally arranged marriage or an arranged marriage by introduction. This is so that the values and customs are quite similar. The marriage is considered to be between families as much as between the husband and wife. Weddings customarily consist of anywhere from over 300 persons to over 700.

The ethics for relating in the extended family are based on the model of the joint family, where three generations live together with the possibility of aunts and uncles and their children as well. Formal hierarchical relationships of age and gender prevail, with a contextual ethic and morality, *dharma*, generally defining the roles each is to play. However, in contrast to Western morality, *dharma* defines proper behavior as varying with the time, place, nature of the particular hierarchical relationship, and the natures of the persons involved. It is a highly contextual ethic, similar to Confucianism. One can easily observe Indians saying different things on the same subject to different people. To be consistent as one would expect in a Western context, is to be considered immoral. Thus, the Western ethic, "do unto others as you would have them do unto you" is changed to, "do not do unto others as you would have them do unto you because your natures may be different." Adding to the complexity of the formal hierarchical relationships are the natures and abilities of the different family members, so that a younger son for instance may assume greater responsibilities and have more of a voice than an older one; or a wife while being deferent to her husband may nevertheless be more respected by him and others.

It is further assumed that not only parents but also older siblings will fulfill their responsibilities and care for younger siblings. I have had more than one woman patient

complain about her older brother not fulfilling his responsibilities for her. Veena, for instance, had an excellent position in one of the national ministries and was finishing her doctoral studies at Columbia University, but she was unmarried in her early 30s. This was in the 1980s when this was highly unusual, and her age was considered detrimental to her getting married. She had asked her father to postpone an arranged marriage when she was in her early 20s so she could undertake an important postgraduate program to advance her chances for a career. The father agreed, but soon after she finished, he suddenly died. It was then in her older brother's hands, and he did nothing. She had intense bitter feelings toward him. What kept her going were astrological predictions that she would have a very late but excellent marriage. In spite of great efforts to search for a suitable husband through the Indian newspaper in New York City, nothing worked. A couple of years later, after she had stopped coming for therapy, I ran into her at Columbia University. She was indeed married to a man who met her rigorous standards that he be able to socialize in her ongoing, high-level community, related to the ministry she worked for in New Delhi, and he had to have gone to one of the elite boarding schools in India, and then either to Oxford or Cambridge. She simply met him when he was sitting next to her on a flight to an upstate New York City.

Hierarchical intimacy relationships or the caring or concern for each other with considerable warmth are the important norms for Indian families, although not always fulfilled. As mentioned earlier, rivalry among brothers is kept in check by the senior male(s) of the family, but they may surface later in intense law suits when the father has died. As alluded to before, family reputation is central, how the family reflects on each of its members, and how each contributes to the reputation of the family.

Some years ago, a very capable woman psychoanalyst from our institute referred to me an Indian man in his late 20s, as she had become enraged at his male chauvinism, wanting to divorce his American wife although they got along very well. What emerged in sessions is that he graduated from a good college in North India in the 1980s but was unable to find a job for a couple of years. He then came to New York City on an H1 Visa to work for an uncle, who thoroughly exploited him, making him work long hours for less than the minimum wage. If he quit working for his uncle, he would lose the H1 Visa and have to return to India to face further unemployment. He met and then married a divorced American woman with a child, was able to get a Green Card and leave his uncle's employment to set up a business of his own. He worked long hours, was very successful, and was able to send significant amounts of money home to his parents. This boosted his and the family's reputation considerably in the community. He was the star of the family, but there was just one problem. Coming from a high-caste family, being married to a divorced woman with a child was considered to be an enormous blot on the family reputation. Although he was still in love with his wife and appreciated that through his marriage he was able to make an excellent living and contribute greatly to his family's reputation, he nevertheless was still seriously considering divorcing her to remove the blot.

The Japanese family is structured differently from the Indian family, with the eldest son being brought into the family business or occupation, generally living with his parents, and the younger sons having to leave the family and frequently go into a different occupation. The daughters, as in India, leave the family for the husband's family. Until recent years, women and men were to have one career only, with child-rearing being considered a career. Now, there are a number of professionally trained women who also marry and have children.

Indian and Japanese child-rearing from earliest infancy differs significantly from the norms of American child-rearing. There is greater physical closeness with the infant and young child sleeping next to the mother at night. When another child is born, the older one will then sleep with an older sibling or someone else in the family, if it is at all possible. To sleep alone in a separate bedroom, the ideal of American child-rearing, is considered dire punishment. I have had a few Indian patients, usually the youngest of their siblings, sleep next to the mother until they were 10 or 12 years old. One social worker said she went from her mother's bed to her husband's bed at age 19.

There is multiple mothering in Indian families, including the mother-in-law in North India, the mother in South India, sisters-in-law, aunts, older female cousins, servants, and neighbors, while the mother remains central, although deferent to her mother-in-law or mother. The first few years of childhood are considered to be very indulgent from a Western perspective. When the toddler does something that the mothering person considers inappropriate or dangerous, she does not set firm limits or say, "no," as is done in the United States. Rather, she distracts the child with something else.

One time after a seminar at the South Asian Institute at Columbia University, I overheard a conversation between an older American woman, the wife of the former director of the Institute who had spent substantial time in India with her husband, and a much younger Indian woman, a well-known writer, who had a toddler. The former exclaimed, "How can you not say 'no' to your child? Suppose he is about to run into the street with cars coming!" The former retorted, "I can never say 'no' to him," thereby causing considerable consternation in the American woman. What she did not add is that she would distract her child with something else.

In another instance, a patient, Meena, who was in a doctoral clinical psychology program, came into session

one day exclaiming she was a terrible mother. All of her psychology books assert the importance of mothers setting firm limits on their young children, something which she felt totally incapable of doing. She, herself, had come to the United States with her parents when she was 5 years old, leaving a large joint family in North India. I asked her if she had any memories of how she was raised, whether firm limits were set for her, or whether they simply distracted her when they felt she was doing something potentially harmful. She thought for a moment and then confirmed it was the latter.

A couple of years later as she began to realize the differences in child-rearing, she related the following incident. She was called in by the teacher of her 4-year-old daughter's nursery school class for a conference. The teacher praised her daughter endlessly; she was such a delight to have in class, but there was just one problem. Her daughter kept hugging the other children, who did not like it. Could she get her daughter to stop this inappropriate behavior? When she came home, she told her daughter that it is perfectly fine to hug other children when they are with their Indian friends but not to do it with American children who are not used to it. Thus, she contextualized the situation for her daughter without reprimanding her in the least.

In the 1990s, a research video was shown at the midwinter meeting of the American Psychoanalytic Association in New York City on Japanese and American mothers with their 18–24-month-old toddlers. Dr. Calvin Settledge, a highly regarded child psychoanalyst with a Japanese American student in training, had set up a research project in which one by one Japanese mothers and American mothers with their toddlers were in a playroom. The mother would first be interrupted by a phone call, a little later by someone visiting, and still later, she would be asked to leave the room for a short while, leaving the toddler with a visitor. The aim was to show how the mother and her child reacted to the interruptions. Dr. Settledge, noted for his work in Margaret Mahler's theory of early childhood symbiosis and separation-individuation, was astounded by the results. The American mothers, when interrupted by a phone call or by a visitor, simply encouraged her child to play with toys in the playroom while she spoke with the other. When she was asked to leave the room, she willingly did. Not so the Japanese mothers. When interrupted by the phone call or visitor, she never took her eyes off of her child, and when the child came back to her, rather than encouraging her toddler to go play with the toys, she simply scooped him or her up on her lap and held them. Nor did any of the Japanese women leave the room. The closeness between mother and child was never interrupted.

If the early years from infancy through age 4 are ones of continual closeness and gratification, what I have originally termed "symbiotic reciprocity" in contrast to Western "separation-individuation," after ages 3 or 4, there is widespread agreement that there is a crackdown for proper behavior to observe the social etiquette of the hierarchical relationships of the family. This crackdown continues through adolescence, sometimes with physical punishments, or being yelled at, or being shamed. In India, this is first implemented by the women of the family, then by the men. The mother welcomes the help of her mother-in-law and others when the child is an infant, while overtly deferring to her mother-in-law. However, as the child becomes older, she more and more assumes a central role in guiding the child, and she becomes a mediator between the children and their father. In North India, while daughters marry out into their husband's family, sons, especially the oldest, may stay at home and help their parents. In any case, sons never lose their privileged closeness to their mothers, bringing about a different reading of the Oedipus complex. In Indian mythology, it is not the sons killing their fathers but rather more the reverse. In actuality, sons deeply need their fathers to offset engulfment by their mothers and other woman of the family.

Another matter of significance in Indian child-rearing is that while there is a clampdown for proper behavior for meeting the social etiquette of hierarchical relationships, there is also a great respect for a child's idiosyncracies, much more than in Western countries. The Indian assumption is that the child is born after having multiple past lives with an accumulation of experiences. Therefore, these past experiences and tendencies will show up in his or her nature.

THE FAMILIAL SELF

When we speak of the self in the United States, or for that matter most of Europe, and in our psychoanalytic and psychological theories, it is taken for granted without reflection that it is an I-self. It is not that we do not have important relationships, but it is from one I-self to another. This is not the case in both India and Japan, where there is a we-self deeply enmeshed in familial relationships in both countries, and for men in Japan in group relationships as well. In these we-self relationships, the person experiences themselves as being quite different from one relationship to another. Consistency is not valued, and in fact, two Indian women exclaimed against being consistent. Veena, a patient, could not understand American women's struggle with both having a career and a family. She is a painter who also teaches in a college, saying that she values having different selves, one as a painter, another as a professor, another as a wife, and still another as a mother. She would hate having to be the same. Nandita Chaudhari, a professor in the postgraduate child development program at Lady Irwin College in New Delhi, similarly voiced her abhorrence of having to be the same in all situations. This experiential, changing self in social situations is balanced by the stability of the private self.

While self-esteem is an important aspect of the self universally, I find that it is significantly more valued in Asian societies such as India and Japan than in the United States. In fact, it only entered the psychoanalytic field in a major way in the 1970s with the formulation of Self Psychology by Heinz Kohut (1971). He spelled out the foundations of self-esteem as residing in different kinds of self-objects, that is, persons who can empathize with you, or are objects of idealization, or are engaged in the same activity with you. During a weekend day in Hiroshima devoted to discussing Self Psychology, I was asked why it had taken hold in the United States. They had read Kohut's books but could not understand their significance. I thought for a while and then asked if they had ever seen the paintings of Edward Hopper. Marvelously, Dr. Tatara, who had trained in New York City, had taken slide pictures of a Hopper exhibit at the Whitney Museum, and he showed them after lunch. It became very apparent that the people in the paintings were hardly engaged with one another, similar to the painting of "Christina's World" by Andrew Wyeth. The paintings express an isolated, lonely feeling. It was then easy to say that Kohut's emphasis on adult's empathy with each other and their children, also serving as objects for idealization, and alter ego objects for doing tasks of one kind or another with each other, is very relevant in the United States, where by and large relationships are relatively fragile. In Japan as in India, there is a much stronger emphasis on *omoiari* or concerned empathy. It smooths relationships in the family and in groups. Further, in these hierarchical societies, there is always someone to idealize, if not living then deceased. In India, you also have the gods and goddesses, and holy men and women. In my clinical work in both countries, I found while self-psychology was very pertinent, there was significantly less deprivation of missing self-objects than in my patients in New York City.

In India and Japan, one must speak of we-self-esteem, as the experiential self is different. In general, I found that there are unusually high levels of we-self-esteem, and threats to that is what is to be avoided. At conferences, the majority of people there may not be that interested in the subject but want to support the person speaking, whom they know. Further, there will be far less criticism or challenges to the speaker than at a conference in the United States. In 1977, I attended the International Association of Child Psychiatrists in Ahmedabad, India. I asked one of the American psychoanalysts how this conference went when it was in Israel two years previous as compared to then. He replied that there is no comparison, that in Israel there was constant questioning, criticism, and disagreements, but here everything is peaceful and friendly. I knew, however, that hidden from view there were major disagreements among some of the Indian psychiatrists, but nothing was aired so that they would not be criticized or embarrassed in public. Maintaining each other's esteem was more important than the truth of any given matter.

This surfaced in session when an American patient, an important scientist in his field, was negotiating with a Japanese company. He met one of the Japanese scientists who told him of a theory he had formulated. The American then spoke with another Japanese scientist and told him that the theory he was told was totally wrong according to a great deal of evidence. Since the first Japanese scientist was a well-known person in his field, the second one simply said, "Well, you never can tell."

As mentioned earlier, the Indian conscience is oriented around *dharma*, and the Japanese one is around Confucian values. Both are highly contextual, depending on the nature of the relationship, the hierarchy, the setting, the natures of the persons involved and such. It is much more oriented toward the ego ideal of how one should be in a number of different situations and relationships rather than a more universal ethic.

Japanese appear to have a much more rigorous ego ideal than Indians, or for that matter Euro-Americans; everything must be done to perfection from human relationships to skills and tasks. One Japanese analyst confided to me that in spite of several years of his own psychoanalysis, he still feels beset by the inner pressure to do everything perfectly. One Japanese patient spoke almost with contempt about American inefficiency.

This high bar of doing everything extremely well is inculcated by the Japanese mother, later implemented by the father as well. In 1977, when we were in New Delhi, I asked the director of The Playhouse School, a progressive nursery school and kindergarten with roots in the Merrill Palmer School in Detroit, if she noticed any differences in the different groups of children, ages 3–5 years old, attending the school. Most were sons and daughter of diplomats from various countries. She observed that the children with the most independent initiative are from the United States; those with the most skills are Japanese; and those with the most interpersonal sensitivity are Indians.

Communication also varies considerably among Indians, Japanese, and Euro-Americans. Indian forms of communication also relate to the dual self structure. When I first began to work at the Indian Council of Mental Hygiene, the senior psychiatrist, a well-liked and respected woman in charge of the seven or eight mental health workers there, suggested that I give a seminar one evening a week; she chose the topic, and we all agreed on the time and place where we would have the meeting. They all seemed to wholeheartedly agree on everything. I showed up on time, but I was the only one who came. The following Saturday at our meeting I asked the psychologists and social workers what topic they would like to discuss. Enthusiastically, they all wanted to talk about dreams and how to analyze them. This time they all showed up.

I have found that Indians communicate on three different levels, which may or may not be in synchronization with each other. In the formal hierarchical relationships with a superior, there is almost always verbal assent to what the superior wants. On another level, there are a number of nonverbal gestures as well as moods to which others are usually finely attuned. Then on the third level, there are the actual behaviors, which may or may not be in agreement with what the person has verbally agreed to. Thus, the social workers at the Indian Council had clearly verbally assented to what their superior, the psychiatrist, wanted. But they showed by their behavior that they really did not agree with the topic she had chosen for the seminar.

In another instance, we asked a woman who was taking care of our children during the day while we worked if she would sit with them that evening as we had just learned of a lecture we wanted to go to. She said, "Yes, I can," but the look on her face was morose. I then asked her if she had other plans that evening, which she instantly confirmed. Again, she observed the proper social etiquette by assenting to be available, but she clearly conveyed her unhappiness through her facial expression. I have found even Indians have sometimes expressed difficulty in reading someone's mind as to what they really want or are motivated to do since verbal agreement is only one mode of communication.

While Western communication is predominantly verbal, with the nonverbal often being dissociated, Indian and Japanese communication is considerably consciously nonverbal. M. Nasir Ilahi, a Pakistani psychoanalyst who trained in London, was initially disconcerted working with English and American patients when he found their communication to be overwhelmingly verbal, something he was not used to. While Indian verbal communication may at times be circuitous, Japanese is overwhelmingly by innuendo. A Japanese pianist who performs both in the United States and Japan stated that he had to learn to be very direct in America, otherwise no one understood him, but to speak by innuendo in Japan; otherwise, they would experience his directness as being insulting.

While Indians do sense each other's moods and such, in Japan it borders for an American on mind reading. In Hiroshima, I was listening to case notes of a Japanese psychoanalyst, Dr. Yoshiko Idei, trained at the William Alanson White Institute in New York City, of her year and a half work with a woman from a very traditional background. I could well understand the psychodynamics of the case and how the woman greatly improved. However, in the length of the whole analytic therapy, there were only two interpretations. Further, Dr. Idei picked up things that were only verbally expressed by the patient 6 months later. When I pointed this out, Dr. Tatara, who headed the group, asked me what I made of it. I stated that it seemed as though Dr. Idei had read the patients mind, and in turn, the patient had read her mind. Another Japanese analyst trained at the White Institute chimed in that this also happened to him when he presented a case there.

In one of the most insightful papers I have come across, A.K. Ramanujan (1990), the late professor of literature and folklore at University of Chicago and the foremost poet in India in English, detailed how Indian thinking is different from that of those in the West. He basically emphasized the contextual, the metonymic, and the monistic in contrast to the European and American emphasis on dualism and universalism. The contextual I have already discussed in relation to the Indian and Japanese conscience. An example of the metonymic is when a statue of a goddess or god is not seen as a symbolic representation of it as in Western thought, but rather as an actual partial manifestation of the god or goddess.

The monistic thinking interconnects everything so that not only mind and body are on a continuum, but the cosmos and individual are too, which is the underlying basis of astrology. This can also be seen in mythic thinking or consciousness. In the broad psychoanalytic field, Jungian psychology tries to get in touch with mythic themes mainly through dreams. However, traditional Indians, especially women, can use mythic characters and themes in everyday life. I once asked the Chair of the Psychology Department and her assistant at NIMHANS in Bangalore if they ever used Indian mythology in their everyday thinking. They looked at each other, hesitated for a minute, and then said, "all of the time"; they gave examples how the various personnel at NIMHANS fitted into their mythic schema, oriented around the characters of the *Ramayana* and the *Mahabharata*, the two great epic mythologies of India.

Ego boundaries and the dual self structure are key components of the familial self in both India and Japan, which I have discussed earlier. I would now like to turn to the issue of individuality and individualism, as I believe there is a great deal of misinformation in this area. Euro-Americans in the modern Western culture of individualism tend to express their individuality in social relationships, in work, in dress, and how they talk and think. In the anthropological literature, they view Asians as having a collective self, implying that they have little individuality. This is not so, expressed two Indian women, Dr. Madhu Sarin, a psychoanalyst, and Dr. Rashmi Jaipal, a psychologist, who have spent years in the New York City area. They claim that their Indian friends, whether in the United States or in India, have more individuality than their American friends. If one accepts the formulations of Self Psychology, then the constant empathic mirroring from childhood on, with many models for idealization, in addition to accepting a child's idiosyncracies as recognition of a nature influenced by past lives, can well develop a strong sense of individuality, while the person is still emotionally enmeshed in insider intimacy relationships. In Japan, individuality on the whole is much

more kept in the private self. Dr. Akahisa Kondo, a Japanese psychoanalyst trained at the Karen Horney Institute in New York City in the early 1950s, once told me, "Our individuality lies in what we do not say."

THE MAGIC COSMIC AND SPIRITUAL SELF

In India, as well as in other Asian countries influenced by Buddhism, there is a fundamental assumption that everyone has his or her own personal destiny, a continuation of experiences from past lives. Further, their personal destiny can be known through astrology, palmistry, psychics, dreams, and such. In their monistic thinking the cosmos is integrated with the personal. And if there is an untoward prediction, traditionally, there are certain rituals or pilgrimages to be done to offset the bad effects. In the West with its strong rational tradition, this is seen as superstition. I have found that even in some American South Asian specialists, although they accept the religious and spiritual traditions of India, they shy away from the magic cosmic. It is mainly in the counter culture in the West that these elements tend to exist, in good part fed by movements such as theosophy and anthroposophy.

I have already cited the prediction for Ashis, my first Indian patient, made on a palm leaf manuscript from his minute of birth over 350 years ago at the Brighu Temple in the Punjab, that his fortunes would take a decided turn for the better when he began seeing me in therapy in February. Another example is an Indian woman doctor, Sarita, who came to me because her husband was extremely verbally abusive to both her and her daughter. She sent the minute of her and her husband's births to a trusted cousin in South India to go to the best astrologer he could find to find out what the astrologer had to tell him about the marriage, directing him not to reveal anything to the astrologer about their marriage. He reported back that the astrologer said to him in effect: Who the hell arranged this marriage? He is a very disturbed man; further, she should leave him immediately as he has something growing behind his right eye, and as it gets worse and he becomes incapacitated, it will be more difficult for her to leave. They already knew he had a brain tumor growing behind his right eye.

Still another example is another Indian woman physician in her late 20s who came to therapy because of entering into what seemed to be an excellent marriage but was extremely unhappy. After going to college and medical school in the United States, she met a man from her own South Indian Brahmin subcaste, who was very successful in his work and came from a prominent family, all of the markings of a highly appropriate marriage. The only problem is that once married, they did not get along. Her mother then requested her to send a thumb print, which her mother brought to a particular South Indian temple where predictions were written over 1500 years ago. When the priest brought out three different palm leaf manuscripts where the thumbprint seemed to match what was on the manuscript, he would first ask the mother to identify the current family makeup. It was only when he said, "Is this the family with an older daughter who went abroad to medical school, and with two younger brothers," which her mother confirmed, that he told her the contents of the manuscript. It described when she would make up her mind, what had caused the current marital difficulty from events in a past life, and what her future life would be like.

One can assert that psychologically Indians, in particular, seem to have a more horizontal and vertical self than most Americans. By horizontal, I mean a we-self more intimately connected to others in the family and community, and in Japan, to others in the family and work groups. By vertical, I mean there is an assumption of connection to past lives in particular and to the cosmos in general.

I have observed that Westerners are now far more open and public about their spiritual practices than Indians who keep this very private. On my psychoanalytic research grant in 1977, I was first attached to the Centre for Developing Societies in New Delhi, a major social science and psychological think tank. At their daily luncheons, which all of the fellows attended, I once asked to what extent is the meditative tradition still alive. The answer was, "You don't know. Even your closest friend may be involved in some meditative practice, but you won't necessarily know about it." Contrast that to an experience in New York a few years later when I was invited to give a presentation. Someone came up to me beforehand and directly asked, "Dr. Roland, do you meditate?"

Among Euro-Americans, the self-creation of one's identity is a fundamental characteristic (Erikson, 1950; Menaker and Menaker, 1965; Menaker, 1982). Thus, for Euro-Americans, being involved in one or another spiritual practice such as meditation becomes an integral part of one's identity. And what is one's identity inevitably becomes public. Whereas for Indians, spiritual practices become part of the private self, usually only to be revealed to like-minded, receptive persons. It enables them to gain some distance and be more evenhanded in their highly emotionally enmeshed relationships.

I have worked psychoanalytically with close to 20 American and Indian patients seriously involved in spiritual practices. My American patients ranged from the majority being involved in one or another kind of Buddhist meditation, primarily Zen Buddhism and Vipassana. Others were involved in Hassidism, Catholicism, and Sufism, the last being a Sufi meditation instructor. What had been an area that was strongly put down within the Freudian tradition for many decades is now being seriously discussed, since for the past 20 or so years there have been increasing numbers of psychoanalytic therapists who are

personally involved in one or another meditation or prayer tradition. Patients involved in spiritual practices seem to handle the anxiety better that is aroused in the therapy process, while simultaneously the analysis helps them in their spiritual practices.

SOCIAL AND CULTURAL CONTEXTS OF WESTERN INDIVIDUALISM

After my experiences in India and Japan, from having to learn the social and cultural contexts of the familial self, I took another journey while home to learn the social and cultural contexts of Western individualism. Paradoxically, this might well have been the most difficult psychological exploration of all. Since everything is so familiar and so silently woven into the fabric of our own psyches and seems so evidently universal, it is difficult to see just how much our own selves are embedded within a whole cultural and historical context. And this pertains to psychoanalysis and other psychological theories as well, all of which appear to be careful, universal scientific statements.

In Western society since the Reformation, the individual has been considered inviolate, the supreme value in and of itself, with each person having his or her own rights and obligations, and each equal to the other. The needs of society are seen as essentially subordinate to the needs of individuals, who are governed by rationality and their own self-interest in mutually consenting contractual relationships. The individual is assumed to be self-contained with considerable social privacy being granted. These cultural valuations of the autonomous individual have come to underlie all of modern European American economic, political, legal, and educational approaches (Allen, 1991; Dumont, 1986), as well as social and psychological theories including psychoanalysis.

Since the Enlightenment, the rational, thinking person has been seen as the most valued, and as intrinsically superior to the person ruled by emotions. Scientific modes of thought that explore causal, logical relationships are seen as primary. The world and cosmos are viewed as essentially secular, that is, knowable through science. All other ways of perceiving reality are discredited as superstition or are demystified, as in the case of religion, magic, and ritual. I detail the historical roots of the culture of Western individualism in Roland, 1996, pp. 4–6.

Psychoanalysis has been in a dialectical dialog with the culture and psychology of individualism, although it is rarely if ever recognized to be embedded in a historical sociocultural context. The critiques today of "the myth of the individual mind" and of a "one-person psychology" are simply not recognized as having their roots in the fundamental Western conception of the self-contained individual. While emphasizing the unconscious and emotions by Freud, and intersubjective and relational theories today, challenging both rationality and the self-contained individual, psychoanalysis in the West still assumes some of the cardinal values of Western individualism: the autonomy of the individual, the self-creation of one's identity, moral values in the conscience to be applied consistently in all situations, relative authenticity in human relations, primarily verbal communication, self-reliance, a relatively consistent I-self, firm outer ego boundaries between self and other, and such.

Whenever anyone emigrates to the United States from a radically different culture, they gradually develop a bicultural self. And even their children, caught between parents from a very different background and American culture and social relations, also develop a bicultural self. On the surface, this can evoke considerable conflict and unease, which can be further augmented by unresolved familial issues.

An example of this is a Japanese woman, Nobuko, who came to therapy for difficult problems she was having in her American company. She had come to the United States a few years previously after attending an elite college in Japan, went through 3 years of graduate studies here, and had a happy marriage to an American. At her work, however, she encountered very upsetting problems that would prevent her from sleeping a few nights in a row. She had decided to work for an American firm, as she felt she could not stand the degree of subordination needed to work in a Japanese trading company. She was expected to deal with her clients in a very direct, forthright way. This was very difficult for her, and when her supervisor directly criticized her for this or one of the very few mistakes she made, far fewer than the other workers, she would become uncontrollably upset. I first pointed out to her the cultural differences between Japanese communication by innuendo and direct American communication, and that she would have to make a decision to what extent she did or did not want to adopt American ways. I also recognized the differences to her between direct criticism from her superior and a more nurturing attitude in the work place at home. As she began putting together a workable bicultural self, what complicated the situation was a powerful grandmother who ruled the roost of her samurai family. Nobuko mentioned that as a teenager she won a National Haiku poetry content. When her grandmother stated, "Of course you won. I write Haiku poetry," Nobuko never wrote another verse. Thus, the clash between cultures within her was greatly intensified by the supervisor's criticisms resonating with the difficult, dominating grandmother.

In the area of diversity, culture is not confined to the different races or radically different cultures. It is much closer to home. One patient, Malcolm, besides having some serious emotional problems due to a father slowly dying of cancer during his teens and his mother then becoming drug addicted, also had a compulsion that we did not understand

for a long time. As a graduate school architectural student with very limited funds, Malcolm would compulsively buy secondhand architectural books at the secondhand book stores in Manhattan. His wife would complain because he never could stop, and it was depleting needed family funds. It was only after more than 2 years of psychoanalytic therapy that I asked for his mother's background. I knew she was Puerto Rican, his father was of German descent, and I assumed she was from one of those Puerto Rican families of not great means that immigrated to the United States in the middle of the 20th century. Instead, he exclaimed that on 14th Street, not far from my office, were stores with Puerto Rican books. He said many of the books of poetry in the windows were written by his elder relatives, that the family was descended from the same family as one of the famous Spanish Catholic saints, that other elder relatives were judges, professors, and such. It then became clear that before his mother had collapsed because of his father's slow decline and death, she had instilled in him as a boy her desire that he grow into a great intellectual. With this realization the compulsion to buy these books greatly subsided.

EPILOGUE

I have wondered over the years why psychoanalysts, with but a few exceptions, as well as psychologists and psychiatrists, have rarely taken into account the sociocultural backgrounds of their patients in seeing the sometimes stark differences in the self, especially across radically different cultures. I found two main reasons.

I first thought that the major reason was the obvious difference between the modern Western culture of individualism dating from the Reformation in the 16th century and the Eastern cultures, which emphasize being enmeshed in extended families and communities or the work group, and the unreflective views of analysts and others that Western norms were both universal and superior. It is clear, for instance, that many of the main concepts and norms of psychoanalysis are oriented toward individualism: for example, separation-individuation, firmly set ego boundaries between self and other, a relatively consistent superego in one's relationships, and overwhelmingly verbal communication. If one were to use the norms and contents of the self across civilizations based on Western values as universal, then one ends up with colonial attitudes of superiority.

In more recent years, after reading a book by Celia Brickman (2003), I came upon another major reason for discounting the cultural and social differences that are deeply internalized. It has rarely been reflected upon that Freud formulated his theories at the height of the colonial era when the prevailing theory was Social Evolutionism. It posited that reason, science, and technology were the markers of the highest social evolution in societies, and that everyone else was inferior, primitive, or savage. Thus, while northern European and North American countries were considered at the height of social evolution, southern Europeans, Slavs, and Jews were seen as inferior, with Asians, Africans, and others being labeled either primitive or savage. Freud reacted by positing psychological universalism, the psychic unity of mankind, thus doing away with this superiority−inferiority continuum. While it was a major advance over Social Evolutionism, it nevertheless discounted the profound variations of persons from different cultures. I have found from being on panels with psychoanalysts from radically different cultures who have been trained in Europe or the United States, that they also adhere to the dogma of the psychic unity of mankind, that culture and social relationships do not have any effect on the inner psychological makeup of their patients. They have, in effect, taken on the identity of their Euro-American colleagues.

REFERENCES

Allen, D., 1991. The social construction of self: some Asian, Marxist, and feminist critiques of dominant Western views of sef. In: Allen, D. (Ed.), Culture and Self: Philosophical and Religious Perspectives East and West. Westview Press, Boulder, Colorado, pp. 3−26.

Brickman, C., 2003. Aboriginal Populations in the Mind: Race and Primitivity in Psychoanalysis. Columbia University Press, New York.

Doi, T., 1973. The Anatomy of Dependence. Kodansha International Limited, Tokyo, New York, and San Francisco.

Doi, T., 1986. The Anatomy of Self: The Individual Versus Society. Kodansha International Ltd, Tokyo, New York, and San Francisco.

Dumont, L., 1970. Homo Hierarchicus. University of Chicago Press, Chicago.

Dumont, L., 1986. Essays on Individualism. University of Chicago Press, Chicago.

Erikson, E., 1950. Childhood and Society. W. W. Norton, New York.

Kakar, S., 1978. The Inner World: A Psychoanalytic Study of Childhood and Society in India. Oxford University Press, New Delhi.

Kohut, H., 1971. Analysis of the Self. International Universities Press, New York.

Menaker, E., 1982. Otto Rank a Rediscovered Legacy. Columbia University Press, New York.

Menaker, E., Menaker, W., 1965. Ego in Evolution. Grove Press, New York.

Nakane, C., 1970. Japanese Society. University of California Press, Berkeley and Los Angeles.

Ramanujan, A.K., 1990. Is there an Indian way of thinking?: An informal essay. In: Marriott, McK. (Ed.), India Through Hindu Categories. Sage Publications, New Delhi and London, pp. 41−58.

Roland, A., 1988. In Search of Self in India and Japan: Toward a Cross-cultural Psychology. Princeton University Press, Princeton.

Roland, A., 1996. Cultural Pluralism and Psychoanalysis: The Asian and North American Experience. Routlege, New York and London.

Roland, A., 2011. Journeys to Foreign Selves: Asians and Asian Americans in a Global Era. Oxford University Press, New Delhi, London, and New York.

Chapter 26

Biological and Social Causation of Serious Mental Illness

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The most effective health systems are built on an evaluation of the needs of the population, scientific understanding of the illnesses that are to be treated, and the development of a balanced set of interventions in health promotion, illness prevention, and evidence-based, or evidence-informed, treatment.

Fundamental to the development of effective interventions is an understanding of the cause of an illness. The World Health Organization (WHO) has amassed an impressive array of evidence-based strategies for prevention (Hosman et al., 2005) based on an understanding of causation. This mirrors effective treatments across medicine where, similarly, the best health service responses are built on an understanding of etiology. Interventions built on a solid understanding of the factors that increase the risk of an illness and the pathological processes that allow the illness to develop are most likely to be successful. Whether the interventions are to treat a problem, to prevent relapse, or to decrease the risk of other problems that an illness can cause, understanding why a person has the illness and how it impacts on the body give the best chance of success.

Psychiatry has found it more difficult than many other areas of medicine to identify the causes of illnesses. This may reflect the way that mental illnesses are diagnosed, turf battles between researchers as to whether the causation is biological or social, and our ability to understand the human brain and the mind.

Psychiatry is making significant progress on all of these fronts. We are at an exciting time where, from an etiological perspective, many of the elements are in place that could revolutionize the way we think about mental illness and our ability to treat and prevent it.

The research is being undertaken by different groups around the world. It has rarely been collated, but it is agreed that pulling this disparate research into one place helps us to see the possibilities. Our understanding of the causation of the most severe mental illnesses, schizophrenia, and the other psychoses, and the importance of both the biological and social factors involved has increased. Our understanding of the biological mechanisms that link individual and societal risk to actual psychosis are clearer than ever. However, it may be that the development of a simpler way to present what is quite complex theory may help to improve our ability to move from theory to change.

DIAGNOSING MENTAL ILLNESS

Understanding how mental illnesses are diagnosed is important for understanding its etiology.

There are three dominant systems of diagnosis that are used worldwide: the International Classification of Disease (ICD) published by World Health Organization (2015), the Diagnostic Statistical Manual (DSM), published by the American Psychiatric Association (2015), and since the late 1970s, China has developed its own diagnostic system (https://en.wikipedia.org/wiki/Chinese_Classification_of_Mental_Disorders).

Diagnosis of mental health problems is strategic and political. In physical health, all countries use the same WHO diagnoses, but in mental health the United States and China continue to use and refine their own systems.

The ICD is used by more people in more countries worldwide. The DSM is used in the United States and in various countries across the world, but in fewer places than the ICD. The manuals take different strategies for identifying mental illness. The ICD offers guidance but leaves much to the discretion of clinicians, whereas the DSM is

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00026-0

very rule based. In the DSM world, you have a particular diagnosis if you have certain symptoms. Not surprisingly, the DSM is often preferred by researchers, pharmaceutical companies, regulating bodies, and health insurers.

Over time the diagnoses have become more elaborate. The first diagnostic system had one diagnosis, and this was rarely used. The current version of the DSM has over 300 diagnoses, and about 26% of the United States population would have some sort of psychological disorder (see McKenzie, 2013).

The history of the DSM offers an insight into the changing perceptions of what mental illnesses are. It also gives an indication of how difficult it is to identify the causes of mental illness based on current diagnostic systems.

Initial attempts at diagnostic systems in the United States were driven by need and were pragmatic. One of the first official attempts at developing a classification system in the United States was the 1840 census. The need was part of a general trend of governments worldwide starting to take responsibility for the mentally ill. States were building huge hospitals, so getting a handle on the possible volume and cost of this enterprise was important. There were two categories in the New York State system: sane or "idiocy/insanity.n The government was not interested in complex ideas of the psyche or symptoms of depression. They were interested in which people could not function in society and may need the government to support them.

From the etiological perspective, "idiocy/insanity" is such a broad concept that it is likely to include many different illnesses and disease processes. It is also linked to the ability of a person to function and because of this to the context a person lives in. Trying to identify the cause of such a broad concept, which is likely to include a variety of illnesses, would be obviously be challenging, if not fool hardy. This is clear when the system is basic, but the difficulty remains when diagnostic systems are more complex.

By 1917 with mental hospitals full, the National Committee of Mental Hygiene and members of what was to become the American Psychiatric Association (APA) decided it might be useful to have more than one diagnosis because they noted differences between the patients who were in their institutions. Based on the belief that producing a number of different categories of patients—or diagnoses—would help them develop better treatments for those who were institutionalized, they developed the "Standard" a statistical manual for use by institutions. There were 22 diagnoses.

Diagnoses in the Standard were based on descriptions of symptoms. As such the categorization was based on how an individual presented their problems. There was little attempt to consider how problems came about, and there was little understanding of the pathological processes involved. Given that very different mental illnesses can have similar symptoms and signs, basing diagnosis on symptoms alone would make identifying cause difficult, even if there were more sophisticated ways of investigating the brain than were available 100 years ago.

The evolution of diagnosis in the United States continued; the American military produced their own diagnostic system, Medical 203, in 1943, to help identify those at risk of problems in war. But the diagnostic game changer came in 1949, and the impetus came from outside the United States.

WHO had for years been publishing the ICD. The ICD categorizes all physical illnesses. For their sixth version, they included a section on mental disorders. But unlike physical disorders, this was not accepted by the United States.

Post-WWII, the United States was in the ascendancy, and the new war was a war of hearts and minds. United States ideas and the export of the American dream were central to the new political landscape. Rather than accept the ICD classification, the United States decided it needed to define the mind for itself. In 1952 the APA produced an adapted version of the Standard and Medical 203 and sent it to 10% of its membership for approval. The agreed document, DSMI, was 130 pages long and listed 106 mental disorders. DSM II was published 16 years later. It was 134 pages and listed 182 disorders.

Both DSMI and DSMII produced diagnoses based on cause. The theories of causation were based on the theories of Freud and other psychodynamic therapists. It was discursive rather than descriptive. It was based on a theory that had been built on observation. It relied heavily on the clinician. Disorders were not detailed but were considered reflections of broad underlying conflicts or maladaptive reactions to life problems. Diagnoses were subjective.

Despite the fact that Freud was a neurologist, there was little attempt to identify any physical substrate of an illness. The causes of different mental illnesses were considered to be psychological and were linked to a variety of problems in the development of the psyche and the regulation of basic human drives by our consciences. The theory was that the cause of mental health problems lay in attempts by society to socialize us.

Psychodynamic theories of causation try to investigate the interaction between the individual and their environment. Whether or not they have eventually been considered a useful basis for diagnosis, the fact that they are an elegant attempt to link the individual, their context, their environment, and their history as a way of conceptualizing categories of illness is light years ahead of some of the more reductionist approaches that have followed. Whether, you agree with their formulation of causation or not, they are trying to include most of the important elements that we know lead to mental health problems into one conceptual framework.

The aim of the DSM system was to make it easier to identify specific problems, to ensure that diagnoses were made in a standardized way across the United States, and like other systems to help those who were trying to understand which treatments work for whom and what the likely outcome was of a particular set of symptoms. Unfortunately, DSMI and DSMII were difficult to use. There was significant variability between psychiatrists in how people with similar symptoms would be diagnosed, and there were added issues, such as the fact that homosexuality was classed as an illness. It was not clear that they were useful for deciding on treatment. Change was needed (see McKenzie, 2013).

DSMIII was published in 1974 to improve the uniformity and validity of psychiatric diagnosis. Psychodynamic theories of pathology were abandoned. The group used a more scientific approach to define psychopathology and identify patterns of disease through their chronology and outcome. Diagnoses were constructed using symptom clusters. Cause was not a major consideration in developing diagnostic groups. There was also no need for the symptoms to be causing a problem. If you had the symptoms, you had the illness.

DSMIII was 494 pages and listed 265 diagnostic categories. It is of note that the chair of the committee that wrote DSMIII later criticized his own work saying it led to the medicalization of 20–30% of the population who may not have had any serious mental problems. A revision, DSMIIIR, was published in 1987: 567 pages and 292 diagnoses. And in 1994, DSMIV was published: 886 pages and 297 diagnoses. The latest iteration is DSM5: 987 pages and an extra 15 diagnoses on top of DSMIV.

Each has tried to improve the repeatability of the diagnostic process and the utility of the manual. For instance, because of criticisms of DSMIII, that symptoms alone did not necessarily mean there was a need for treatment, in DSMIV having symptoms alone was not sufficient for a diagnosis. Symptoms or diagnoses had to cause "clinically significant distress or impairment in social, occupational, or other important areas of functioning" for them to be relevant.

A shift like this may be clinically appropriate, but it leads to problems for those trying to identify the cause of an illness. This is because whether you function or not depends on what you are asked to do or need to do. Two people with the same symptoms (presumably the same illness and the same cause) may get different diagnoses based on whether they can function or not. For instance, if symptoms impeded a person's ability to work, whether this is a problem with functioning would depend on whether they needed to work or not. A person who does not need to work may be less likely to be given a diagnosis than a person who needs to work to survive. And there are similar problems with the impact of social norms on the integrity of a diagnosis. If norms change over time, then the expectations on an individual may also change. People with the same difficulties but who live in different decades or centuries may be given different diagnoses.

DSMV tried to fix this. It characterizes a mental disorder as follows:

> *a clinically significant behavior or psychological syndrome or pattern that occurs in an individual (which) is associated with present distress… or disability… or with a significant increased risk of suffering.*
>
> APA, 2013.

There are many possible critiques of this, but the central difficulty is that current psychiatric diagnoses are based on a system of description of symptoms, chronology, and epidemiology. There are no physical tests to support them. They are groups of symptoms that are linked together by statistical associations and theory.

Unlike physical illnesses where there is often general agreement, the three mental illness manuals have similarities and significant differences. Like the DSM system, they have changed over time.

Because mental illnesses are based on symptoms rather than clear physical pathology, it may be that each symptom cluster could contain a number of different problems with different causes. It would depend on how specific the symptoms were. Using an example from physical medicine, a common symptom like a headache may be caused by many different illnesses: from muscle tension through vascular issues and intracranial hemorrhage to tumors. Each of these problems has a different cause. Of course, on the other hand, there are clinical histories and particular symptoms that we know are characteristic of specific illnesses. We know that from laboratory tests and autopsies. The problem for psychiatry is that in the absence of clear biological substrates it is difficult to know which symptoms signify a group of problems and which are pathognomic.

It could be argued that an added problem for trying to identify the causes of current mental illnesses is the fact that diagnoses are linked to context and societal norms (McKenzie, 2013). But as we discuss newer ways of thinking about etiology, this inclusion of context may be seen as a virtue. But what is important to consider when thinking about the cause of many mental illnesses is that they are syndromes (collections of symptoms) rather than illnesses. Because of this, they may have multiple causes.

THEORIES OF ETIOLOGY

The history of theories of etiology of mental illness are reflected in the way we make diagnoses. We have moved from psychodynamic theories, through theories based on place, and more recently to more biological theories. When

I started psychiatry 25 years ago, there was a clear schism between those who consider mental health problems to be neurological diseases and those who think of them as sociological. These lines of demarcation remain for many. I will outline how we got to this dichotomy and how new ways of thinking will lead us out of it. However, to understand the problem, one has to understand theories of causation in general and then causation in mental illness specifically.

A brief history of causation: Theories of causation have changed over time. Prior to the current theories of modern medicine, the cause of disease was attributed to spiritual or mechanical causes. Illnesses were thought to be due to the elements, humors, or miasma (bad air arising out of dirt and decaying organic matter) (Susser and Susser, 1996a).

The theories that evolved in early public health medicine in high-income countries were built on these theories. Initial theories of causation were place-based. Poor areas, rather than people being poor, were considered to be the cause of many illnesses. Increased rates of illness were because of where you lived rather than who you were. In this way, early public health was environmental and ecological. They focused on urban areas and aimed to improve and sanitize the slums.

Their ideas led to an improvement in living standards and life expectancy that is unparalleled. Their ideas were not based on a sound understanding of what exactly was causing illness; nevertheless, they had a profound impact on our lives. They helped to ensure that there was clean water, sewage systems, safe food, and improved living conditions. The sanitary movement had a more profound impact than many subsequent health interventions (Susser and Susser, 1996a).

Early public health theories were changed by the discovery of viruses and bacteria. Based on current theories of the importance of place, John Snow, considered the father of modern epidemiology, was trying to map the cholera outbreak in Soho, London, England (http://www.johnsnowsociety.org/). He found a small group of people who were outliers; they lived in Hampstead, North London, 6 miles from where most other cases of cholera were. He discovered that these North Londoners liked the taste of the water from Soho, and so got it brought to them. He was then able to identify a specific water pump in Soho that they sent their staff to: it was at the epicenter of the outbreak. Removal of the handle of the Broad Street pump did not only stop the outbreak and save lives, it also led to increased momentum for scientists trying to identify what was in vectors such as water that made people sick.

The discovery of infectious agents has been one of the triumphs of medical science. However, germ theory, based on the discovery of viruses and bacteria, in some ways initially led to a simplification of theories of causation.

There were two issues initially believed by some: whether you got a particular disease depended simply on whether you were infected by a particular germ, and intense study of germs moved the focus of the study of causation out of the field and the environment and into the laboratory. In some ways, initially more disconnected theories of causation based on laboratory findings were developed.

Over time, it became clear that mono-causal germ theory had its problems. Some of the most profound were the fact that exposure did not always lead to illness. Exposure to a particular germ was necessary for a particular illness, but it was not always sufficient. Because of this, other factors needed to be taken into consideration. In addition, exposure depended on how you lived and where you lived.

The epidemiological triangle approach built on germ theory (Mausner and Kramer, 1985). It asserted that disease was a product of an interaction between the agent (the germ), the host (the person), and the environment. The host and the environment determined both the levels of exposure and or susceptibility to the actions of the particular germ. If you wanted to understand the etiology of a specific illness, you needed to understand the germ, the environment, and the person. Lab-based investigation was important but so was the study of the environment.

With the introduction of penicillin and immunization to importance of infections in high-income countries started to diminish. In their place, chronic diseases started to be seen as more significant public health issues. The epidemiological triangle is useful for infections, but its utility diminishes when trying to produce etiological theories for chronic diseases such as diabetes or schizophrenia or degenerative disease. This is in part because these illnesses are characterized by the lack of a single specific agent.

A different approach is often used. The web of causation theory argues that for many chronic illnesses there is no specific agent. There are many different exposures, over time, which produce complex interactions of many factors. These different risks and exposures form interlocking events. Essentially, a person has a number of exposures (or agents), and each has a context (environment). Each person, exposure, and context triad forms an epidemiological triangle. For chronic diseases, there are multiple exposures that are part of the creation of a disease process. Each of these exposures forms an epidemiological triangle. Each of these triangles link to another to form the web of causation for a particular disease (Susser and Susser, 1996a).

It is rare, in chronic diseases, that any particular exposure by itself leads directly to an illness. Generally exposures change the risk of developing an illness and change the risk of exposure to other risk factors. Increased risk can be directly linked to a particular exposure but can also be indirect through the impact that one epidemiological triangle has on others in the web of causation. Just like a spider's web, if you move one corner, you have an impact on the integrity of the whole.

There have been other impacts of this etiological journey. Germ theory, the epidemiological triangle, and the

web of causation have changed the focus from the solely ecological (area) toward the individual (whether it is their vulnerability or their exposure to a germ or a risk factor), and the environment (what in a particular area makes people sick).

A particular development is that the agent in chronic disease can be a behavior or a lifestyle choice rather than an external agent such as a bacteria. Because of this, the risk of an illness is linked very closely to what a person chooses to do and who they are. The environment is included, but often the environment is linked to the individual.

One problem this produces is that individual approaches by themselves may not do justice to the ecological nature of health disparities. This theory has led to some criticism and some alternative approaches. One group are the general theories of susceptibility. These do not identify single or multiple risk factors associated with specific disorders but seek to understand why some social groups are more at risk than others.

The assertion is that because some groups are at generally greater risk to multiple disorders there needs to be a theory to explain this at a group level rather than an individual level. The question that these theories try to answer is this: is there something about what is happening to the group or at the group level that could be causing differences in rates of illness and therefore differences in risk of illness for an individual?

The theory of fundamental social causes is a good example of a general theory of susceptibility. It neatly links the various theories of disease etiology together and comes full circle to reinvigorate ecological perspectives (Phelan et al., 2010).

Considering health disparities is an accessible way of introducing and considering the challenges of the fundamental social causes theory. In high-income countries, 100 years ago, disparities in life expectancy between rich and poor were mainly because of infectious diseases. Put simply, the poor lived in situations such as the rat infested, overcrowded slums of cities where they were more likely to be exposed to and to contract infectious diseases. In addition, they were less likely to get effective treatment.

The impact of infectious diseases and the disparities in life expectancy because of them have been decreased with the advent of modern sewage systems, clean water, vaccination, and the development of antibiotics. However, disparities such as the difference in morbidity and mortality between rich and poor in high-income countries have remained.

Instead of differences in life span and rates of illness being because of infectious diseases, they are now linked to chronic diseases, such as diabetes, high blood pressure, cardiac problems, and cancer.

The fundamental social causes theory of etiology states that disparities between rich and poor are due to social factors such as power, money, and access to information. Increased rates of specific diseases linked to the action of specific agents, behaviors, lifestyles, or exposures are because of the action of these fundamental social causes rather than because of the specific agents, be they germs or the behaviors or choices of individuals.

One of the utilities of the concept of fundamental social causes as a driver of disparities is that it allows a focus on what needs to be done at a group level to decrease the rates of illness. The risk of an individual can be modeled as being because of who they are and what they do, but who they are and what they do is determined in part by the structure of society.

A further, important issue that flows from this theory is that ignoring the fundamental social causes leads to ineffective intervention. It is possible to produce successful interventions against the diseases currently linked to disparities, but over time, there may be little impact on disparities between groups. There are many reasons for this; one is that many public health interventions (ie, screening tests and preventive medicine) are more likely to be taken up by those with power, money, and access to information. Another issue is that the fundamental social causes will find another avenue through which to express themselves. Treating current problems may decrease the impact of that particular illness, but new problems may ensure that disparities continue, such as happened when chronic diseases took over from infections as the main cause of differences in life expectancy in high-income countries.

General theories of susceptibility are useful, but the most successful etiological theories seem to have been to build on previous theories. Rather than producing theories that are in opposition to each other, producing a new theory that encompasses previous theories has proved more profitable. For instance, early public health theories of causation were built on prior place-based theories, and it could be argued that the web of causation was built on the epidemiological triangle. Given this, linking theories that focus on the individual and theories that focus on the group or ecological level could be a useful way of better understanding causation in a complex world.

An elegant theory that pulls these different strands together is the Chinese Box or Russian Doll model of causation (Susser and Susser, 1996b).

This theory posits that rather than being a group of epidemiological triangles or risks at the same level, a disease is caused by interconnected but separate levels of causation. Each of these levels of causation can be considered a Russian Doll.

The theory in its essence is that, rather than being a single web of causation, there are a number of webs working at different levels. Each of these levels can be thought of as a Russian Doll. Each fits inside the other. Levels move from lower, more internal levels such as our molecular biology, and they can be considered at a number of different levels (eg, genes, organs, organ systems,

individuals, the interpersonal space, and higher levels such as societal factors). These levels have different sciences and are investigated in different ways: using methods in molecular genetics to investigate urban policy decisions may not prove that fruitful. In general, the amount of variance at a lower level is constrained by the level of variance in the level above it. So, though there are some diseases in which the individual genetic risk outweighs most other factors, for chronic diseases with complex etiologies, the impact of the environment and context on the rates of illness are often greater than biological processes.

Because of the way scientists tend to work, our understanding how the different levels interact is underdeveloped. This is partly because there are difficulties in getting different sciences to speak to each other but also because understanding how different types of science interact is challenging.

A further nuance to the Russian Doll theory comes from the four dimensions model (Shah et al., 2011). This model understands that for practical purposes it may be worth thinking of the different levels of the Russian Doll model into two: individual and ecological. It then specifically acknowledges and includes the possibility that ecological influences such as fundamental social causes can have an impact on individual causes. And then, it includes the concept of time. The four dimensions are individual, ecological, interactions, and time.

The simplification aims to focus discussion on the different elements of an etiological process and to produce an architecture for investigation as well as a simplified model that may help intervention. It aims to be practical.

Different levels of causation have been discussed earlier when outlining the Russian Doll theory. The fact that levels may interact may be obvious, but specifically allowing for it aims to ensure that it is not forgotten. Time is considered important because different processes may have different chronologies: for instance, there may be sensitive periods in which people or groups of people are particularly sensitive to certain environmental exposures (eg, when you are young or when you are old), there may be different lengths of exposure needed to cause a problem, there may be a lag time between exposure and the development of an illness, and of course, different process at different levels may have different "time spans.i The understanding of causation may in part be helped by understanding how these different chronologies overlap. Moreover, there may be times when the environment is particularly sensitive to the actions of people and that may change the risk of illness. The current impacts of human on global warming are more acute now than they previously were. Similarly, the impact of the actions of humans on the social environment changes at different times in the history of a country.

In summary, the history has been that public health was "ecological" in its origins; the advent of germ theory led to a uni-causal theory of disease. Initially, environment as a whole was considered, then specific factors within the environment that promoted illness. There had been a progressive individualization of risk: a perpetuation of the idea that risk is individually determined and a dissociation of risk from social contexts. Modern theories have tried to balance individual risk factor analysis with ecological analyses of causation. Including time allows for a deeper understanding of the multilevel causation of illness in an environmental and historical context.

MENTAL ILLNESS AND BIOLOGY AND ENVIRONMENT

A deeper understanding of etiology is important when trying to investigate the causes of mental illness. For many mental illnesses the idea that there are biological, psychological, and social factors that contribute is not considered contentious.

Most people are happy to accept that more common mental illnesses such as depression and anxiety may run in a family. This would imply a genetic contribution. Most people would also likely agree that certain drugs might cause depression and that hormonal changes, for instance at puberty or at the menopause, can also spark a depression. Few would have a problem with the idea that you can become depressed because of a physical illness. The list of agreed biological causes is long and not contentious.

Similarly the list of social factors that are considered possible causes of depression is extensive. They are essentially "loss" events and include being fired from work, being evicted, being imprisoned, breaking up with your partner, loss of other family members, etc.

Other theories suggest that there can be a mindset that promotes depression. The idea of negative thinking is one populous iteration of a number of possible psychological processes that may increase vulnerability to depression.

If asked to reflect, I would imagine that many would have little problem with the assertion that depression and anxiety can be caused by a complex array of biological, social, and psychological factors. This is well reflected in the Wikipedia page on the causes of mental illness (https://en.wikipedia.org/wiki/Causes_of_mental_disorders).

There is less agreement on the contribution of biological, psychological, and social factors to mental illnesses that are often more persistent and severe such as schizophrenia and other psychoses. Again, this disagreement is well reflected in the Wikipedia page (https://en.wikipedia.org/wiki/Causes_of_schizophrenia).

However, surprisingly, understanding the current scientific directions and findings of the causation of schizophrenia and other psychoses gives an exciting lens to the way that social factors get under the skin and allows the exploration of how the newer models of causation work in the real world.

Schizophrenia

Schizophrenia and other psychoses are substantial public health problems that impose a profound impact on national economies, health and social systems, affected individuals, and their families and caretakers.

Schizophrenia is a chronic illness with a 0.5−1% risk in lifetime. Its huge costs to society are often linked to healthcare and welfare costs, but the major impact is on individuals and families.

However, schizophrenia is as much a concept or syndrome as an illness. There are no medical tests for schizophrenia or other psychoses. The diagnosis is based on the symptoms that are presented and the lack of a physical cause for the problems. The symptoms of schizophrenia can be caused by many other medical illnesses: from brain tumors to serious infections. They can also be caused by intoxication by drugs. But when characteristic symptoms are present and no other cause can be discovered, the diagnosis of schizophrenia is made.

The symptoms vary: they include delusions, hallucinations, problems with control of thought, social withdrawal, cognitive impairment, and depression. There are a number of other illnesses that have similar symptoms but not all the symptoms that are required for a diagnosis of schizophrenia. Over time, many people whose symptoms fall short of being diagnosable for schizophrenia eventually present with enough symptoms for a diagnosis to be made. Because of this, some researchers feel it is better to consider schizophrenia and other psychoses as one group of illnesses. Of interest, others still, such as the past head of the National Institutes of Mental Health in the United States, believe that diagnoses are not accurate for research and have suggested that looking at the cause of individual symptoms may be a better approach (Insel, 2015).

Schizophrenia and the other psychoses are considered a more severe form of mental illness because, during acute presentations, individuals may seem to have lost touch with reality. They may be hearing voices when no one is there, they may be responding to thoughts that have little clear basis in reality, and they may have difficulty knowing where they begin and end. For instance, some people may think during a severe episode that other people can read their mind or place thoughts into their head. The problems often start in the teenage years, and there is only 30% full symptomatic recovery; for some, there is a gradual decline in their ability to advance themselves in the world. Many people with a diagnosis of schizophrenia do not work, though this is as much because of stigma as their capabilities. On average, in high-income countries, the life expectancy of a person diagnosed with schizophrenia is decreased by 20 years because of comorbidities such as smoking, poor diet, the impacts on medication to control symptoms on the metabolism, and suicide. The risk of suicide in schizophrenia is higher than the risk of suicide in depression.

The diagnosis of mental illness and the treatment offered is based not only on the symptoms present but also on the impact that those symptoms have on an individual and the community. Generally, there is a need for symptoms to lead to suffering or problems in function for them to be considered a mental illness.

The treatment of schizophrenia and other psychoses includes medication, psychotherapy, family therapy, social interventions such as work and appropriate housing, and interventions to counter any cognitive decline, if there is any.

The treatments for psychoses are good, but even with excellent medical care the prognosis for many is not good. Interventions do not aim to cure psychoses; they aim to treat symptoms and support individuals. Long-term medication may help to prevent relapse, but there are side effects.

In such cases, an ounce of prevention may be a better approach. The best prevention strategies are based on an understanding of the etiology of an illness.

The idea that schizophrenia and other psychoses could be preventable may be surprising to some. This is in part because WHO's International Pilot Study of Schizophrenia in the 1970s suggested that the rates of schizophrenia were essentially the same across the world (Sartorius et al., 1974). However, more recent attempts to investigate and collate incidence rates of schizophrenia using standard measures have reported significant differences between and within countries (McGrath et al., 2008). If you can identify the reasons for differences in rates between groups, there is a possibility that you can find a strategy for prevention.

As with many chronic illnesses the causes are complex and work at many different levels. Recent advances in our understanding of the pathophysiology of psychoses such as schizophrenia have focused on the brain mechanisms that underlie particular symptoms in the search for improved pharmacological treatments. This may have inadvertently supported the perception that psychoses are "brain diseases" and that the impact of social determinants may not be relevant. But the borders between the brain and the environment are being eroded by newer evidence on causation.

Balancing the development of our biological understandings, there is a growing literature outlining the associations between a number of social or societal variables and the onset, course, and outcome of psychosis (Morgan et al., 2008).

Rather than use these two sciences to better understand the etiology, at times, it seems like studies and the papers written from them have fueled an etiological arms race, with biologists and social scientists building their arsenals of knowledge in the battle for superiority and, presumably, grant funding.

The understanding of the etiology of schizophrenia and other psychoses may benefit from the approach in medicine in general where etiological ideas have built on each other over time and the focus has been on the unique contribution of different types of risk and etiological pathways rather than which is more important than the other.

The dichotomy between those who focus on the brain and those who focus on the environment produces conceptual difficulties because mental illness straddles both.

Biological Risk Factors

Biological theory of the development of schizophrenia is that the symptoms of schizophrenia are a consequence of a fault in the brain's neurotransmitter systems. An imbalance of specific neurotransmitters in specific regions leads to psychotic symptoms.

Dopamine, glutamate, serotonin, and other neurotransmitters have widespread impact on the activity of brain cells in various parts of the brain, including the limbic system and part of the prefrontal cortex of the brain, which have been linked to emotions and thought. A number of findings including increased dopamine synthesis in specific brain regions, increased dopamine release in the response to every day stimuli, and increased dopamine in the synapses between nerve cells have been linked with the development of psychotic symptoms. Other neurotransmitter pathways are also involved. It is believed that these other systems diminish may regulate the impact of dopamine dysfunction. They regulate the brain response to new stimuli but also decrease the suppression of activation in response to repeated stimuli, thus potentiating the action of dopamine in causing symptoms (van Os and Kapur, 2009).

There is a significant and compelling array of evidence to support the biological processes that are involved in psychosis. They confirm that the symptoms are linked to dopamine. Imaging studies have demonstrated that there is overactivity of dopamine in the limbic system and prefrontal cortex in people with acute psychotic symptoms; studies have been able to replicate psychotic symptoms using drugs that increase the amount of dopamine in the brain; and drugs that block the dopamine and other neurotransmitters have been found to decrease the severity of psychotic symptoms.

However, how the disruption of the neurotransmitter system comes about is less well delineated. Epidemiological studies have linked the development of psychotic symptoms to acute medical problems. Psychotic symptoms can be seen in a number of physical medical conditions including stroke, brain infections such as encephalitis, brain tumors, and in intoxication or withdrawal from drugs. It can also result from other direct insults to the brain. However, there is also evidence that the psychosis can be the result of an insult to the developing brain. This leads to aberrant development of the neurotransmitter systems, which increases its vulnerability to malfunctioning in later life.

How, exactly these impacts lead to psychosis is not clear. Much of the work at this stage has been in assessing which factors increase the risk of psychosis.

There are many biological risk factors linked to the development of psychosis. The aim here is not to comprehensively catalog all of the risk factors but to give an indication of some of the main areas of research to help in the understanding of theories of biological causation (van Os and Kapur, 2009; van Os et al., 2010 for reviews).

Genes: There is a clear genetic vulnerability to psychosis. Essentially, the literature shows that the more genes you share with a person who is diagnosed with schizophrenia, the more likely you are to be diagnosed yourself. This work has been used to argue that schizophrenia and other psychoses are, at least in part, biological in nature. Studies are clear: the risk of schizophrenia in the identical twin of someone with a diagnosis of schizophrenia is 50%. As the proportion of shared genes with a person who has developed schizophrenia diminish, so does the risk: 17% chance for a non-identical twin, 9% for a sibling, down to 2% for first cousins. The search for a specific gene for schizophrenia has been long and not that fruitful. There are groups with specific single gene problems that have a high risk of developing psychosis, but this is the exception rather than the rule. Though a family history of schizophrenia and other psychoses increases the risk of developing a psychosis, in clinical practice the majority of people who are diagnosed have no clear relative with a similar diagnosis. Some geneticists will claim that the vast majority of psychosis is genetic and that this is due to new genetic mutations, but given that genes modulate our biological processes, it is not clear whether they are referring to the cause of psychosis or the mechanisms. It is also not clear what causes these mutations. What is clear is that there are multiple genes involved. Given the fact the identical twin or someone with a diagnosis of schizophrenia will have very similar genes but only 50% chance of developing schizophrenia, some would argue that this is a genetic problem of incomplete expression. In many genetic problems, genotype (what genes you have) and phenotype (how the genes are expressed) are not 100%. The expression of the genotype may depend on a number of different things.

An easy way to think of this is in tanning. Whether your skin tans or not in the sun depends in part on your genes (your genotype for tanning), but whether your genotype is expressed as a phenotype (whether you have a tan) may depend on your exposure to the sun.

Obstetric complications: Another biological risk factor is obstetric complications. Studies have reported that babies who suffer obstetric complications such as prolonged labor or periods of hypoxia during birth have an increased risk.

One theory is that hypoxia may impact brain development and that the pathways that are involved in the development of psychosis are particularly sensitive to hypoxia. Hypoxia decreases the resilience of the neurotransmitter pathways and so makes them vulnerable to the development of psychotic symptoms in later life.

That damage to the brains of children and young people increases the risk of later diagnoses of schizophrenia and other psychoses has been demonstrated in epidemiological studies. A number of different types of injury including head injuries in childhood, encephalitis, and meningitis have all been linked to increased rates of schizophrenia in adult life. They have been linked to an increased risk of dysregulation of your dopamine pathways, thus an increased risk of developing schizophrenia.

Seasonality: One intriguing line of investigation has come from reports of differences in risk of developing later schizophrenia linked to the season of month of birth. In the northern hemisphere, those born in spring have the highest risk of developing schizophrenia, and those born in autumn have the lowest risk of developing schizophrenia. The risk months are inverted in the southern hemisphere; northern hemisphere high-risk times are southern hemisphere low-risk months.

Seasonality has also been reported in other medical conditions. These have been linked to environmental factors that change with the seasons. For instance, there are many infectious diseases such as influenza that are more likely in winter, and some affective disorders are linked to light, thereby increasing when days get shorter.

Though differences in risk have been demonstrated for schizophrenia, how this links to seasons is not clear. It could be that similar environmental risk factors lead to increasing rates of psychosis and also increased rates of other illnesses such as influenza. However, it may also be that the increased incidence of other seasonal illnesses in some way increases the risk of schizophrenia and other psychoses.

Researchers have investigated viruses with patterns of seasonality, such as influenza, and found variable associations with schizophrenia. Some studies have claimed to demonstrate this link, while other studies have not. The theory linking infections to schizophrenia is that in utero exposure could have impacts on the developing brain leading to increased rates of subsequent schizophrenia and other psychoses in later life. However, the theory is difficult to research because it is not clear at which point in brain development exposure to influenza would lead to a higher risk of schizophrenia. In addition, a serious infection at or around birth potentially could also increase the risk of the development of vulnerable neurotransmitter pathways. A further complication is that other less well-investigated viruses that occur with similar seasonality as influenza may also be important.

Vitamin D: Other researchers have considered other biological factors such as the availability of vitamin D as potential reasons for the seasonality. Interestingly these researchers link vitamin D to influenza. They hypothesize that viruses during pregnancy may lead to vulnerabilities in brain development, or lack of vitamin D may also make individuals more prone to neuronal system malfunction in response to other stimuli. They further link this to the higher reported rates of psychosis in darker skinned immigrant groups in more northern countries. They argue that these groups are vitamin D deficient and so would be at increased risk of psychoses in places with significant seasonality.

Cannabis: A major literature has developed on the impact of cannabis on the risk of psychosis. For over 100 years, there have been concerns that cannabis may lead to mental health problems. This work has crossed the world. This is in part because it was a major concern of the British Colonies; there were major studies in the 19th century in India, South Africa, and the United Kingdom summarized in the Indian Hemp Commission Report of 1894 (http://www.druglibrary.org/schaffer/library/effects.htm). More modern discussion has followed Andreasen's study of 1987. In early adult life, all Swedes are enrolled in military or community service. They all undergo an extensive medical exam at entry. This medical exam includes questions about drug misuse. In particular, it asks about whether cannabis has been used and how many times. Andreasen linked this screening data to health service usage data throughout a person's life. Through this, the study was able to identify all people who were subsequently diagnosed with schizophrenia. The study demonstrated that Swedish conscripts who used cannabis more than 10 times before the age of 18 were at higher risk of developing schizophrenia than those who had not. There was a stepwise increase in risk, so those who had used cannabis 50 times before the age of 18 were at significantly higher risk for developing schizophrenia than others.

There could be a criticism about whether the study demonstrates cause and effect. For instance, a critique could be that studies have shown that differences between people who develop schizophrenia and those who do not can be seen in childhood. In addition, there is a clear prodromal period that can last months to years in which a person may have odd psychological symptoms that are not sufficiently robust to attract a diagnosis of schizophrenia. It may be that people with these troubling prodromal symptoms may be more likely to use cannabis. In this way, cannabis would indicate increased risk but would not cause schizophrenia.

However, there have now been many studies investigating the association between cannabis and psychosis. More recent studies have shown that newer forms of cannabis that are more potent are more likely to increase the

risk of schizophrenia (Di Forti et al., 2009). Unpublished Canadian work has suggested that the correlation between cannabis use and later psychosis is greater than the correlation between any other drug of abuse and psychosis. These two pieces of evidence lead to the conclusion that cannabis itself has some impact on the risk of psychosis because higher concentrations increase risk. And, because no other drug of abuse (neither ones that calm or ones that excite the brain) is as highly correlated, it is difficult to conclude that the link is simply because people are self-medicating prodromal symptoms.

The best analyses to date conclude that cannabis doubles the risk of psychosis (van Os et al., 2009).

However, smart analyses trying to understand cannabis' contribution to the population's increased risk of schizophrenia concluded that elimination of cannabis would decrease the population incidence of psychosis by only 8%. Moreover, as we will see later, the literature also concludes that, though cannabis increases the risk, by itself it is neither sufficient or necessary for the development of psychosis. The impact of cannabis on the risk of psychosis is larger the earlier cannabis is used.

Though the work of groups looking at seasonality, cannabis, obstetric complications, and other biological factors has been at the level of demonstrating associations and to trying to identify what puts people or groups at increased risk, the theories of causation that they have spurned have been complex. They have included environmental factors, multiple other biological factors, and social factors.

Similarly, when associations have been identified between social factors and psychosis, often they have been linked to biological mechanisms when trying to determine possible causation.

The dichotomy between researchers who look at biological and those who look at social or psychological factors may be a fiction (van Os and Kapur, 2009; van Os et al., 2010).

Social Risk Factors

Stress and psychosis: The basis of the social theory has been stress. Stress is a concept that everyone understands but is rarely properly described. Stress is a physiological response to a perception. When we encounter a threat, our stress reaction kicks in, and there are a number of acute changes that aim to improve the ability of the body to either think, fight, or run away. Among other things, attention is increased, blood is diverted to the muscles and away from nonvital functions such as digestion, our cooling system—sweat—is triggered to ensure we do not overheat, and extra sugar is made so that we have more fuel available if we need it. Once we have dealt with the threat, our stress response switches off.

This approach works well when we are faced with a clear threat such as a predator because it allows us to act immediately and quickly to diminish the problem. It works less well in the complex world where we live; the threats we have to deal with tend to be psychological, diffuse, and are difficult to run away from. Even specific life events such as losing a job may have an initial impact, but then searching for a reason, searching for a job, and the possible economic and social impacts are more long-term. Such events turn on our physiological stress mechanisms but often last longer and sometimes do not turn off.

Our bodies are not developed to cope with the impacts of prolonged triggering of our physiological stress mechanisms, and over time, they may harm us. In addition, changes in the body to cope with what it thinks are continual threats may lead to issues. For instance, mobilization of stores to keep the blood sugar level up may harm the adrenal glands and be linked to an increased risk of diabetes. There are numerous other physical illnesses that are linked to continued stress such as hypertension.

There is more detail to the vulnerability-stress model of mental illness (Nuechterlein and Dawson, 1984; Myin-Germeys and van Os, 2008). In general, it posits that genetic or developmental vulnerabilities interact with social adversity to influence a common pathway leading to stress-related effects that may culminate in psychosis.

Genetic, biochemical, and neurological evidence support the link between stress and psychosis (Jones and Fernyhough, 2007).

The biology of the stress response is that perceived stress activates the hypothalamic-pituitary-adrenal axis, which plays a pivotal role in governing our response to threat. The hypothalamus releases corticotropin-releasing hormone, which stimulates the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland into the bloodstream. ACTH, in turn, stimulates the production and release of cortisol from the adrenal cortex, which binds to receptors across the brain and other organs in the body. The binding modulates brain function, immune responses, and cardiovascular function, as well as other processes important in the stress response (Walker et al., 2008).

But if acquired vulnerabilities such as genetic vulnerability, obstetric complications, or social adversity or cannabis misuse are present, the stress response may not work properly. Down modulation of the response may be impacted. The lack of down modulation of the stress response may be linked to the development of psychosis. Vulnerabilities such as a reduced size of the hippocampus in the brain have been found in those at risk or who have psychosis. The hippocampus makes sure that the stress response damps down after it occurs (Fusar-Poli et al., 2007).

In addition, pathways in the brain, which are involved in the transmission of dopamine, are sensitive to stress; exposure to moderate levels of stress can lead to sensitization in individuals, or an enhanced and persistent dopamine response. People who live in stressful environments may be at particular risk of developing a psychotic illness (van Os and Kapur, 2009; van Os et al., 2009).

Life events and daily hassles: Researchers attempting to identify the causes of psychosis have tended to report associations and have mainly investigated risk factors.

In the psychosis literature, initially, there were attempts to understand whether specific life events such as losing a job or other traumas were associated with an increased rate of psychosis. The results of studies have varied but have been presented as demonstrating life events are linked to psychosis risk. The difficulty in this literature may in part reflect the complex nature of the impact of major life events. More recently, studies have investigated a different way that the social environment gets under the skin. Rather than look at rare stressful life events, they have looked at smaller daily hassles. Irritations, such as problems commuting, noise, difficulty paying bills, or with local authorities, have the ability to trigger the stress system and have been more consistently shown to increase the risk of schizophrenia.

Studies have reported that living in stressful neighborhoods where there is social disorganization increases the risk of developing schizophrenia. This may explain, in part, the reports of increased rates of psychosis in urban environments.

Green space: There is a wealth of evidence about the impact of the physical environment on health, as well as a growing literature on its impact on mental health. There is evidence that the level of noise, light, and the quality of the fabric of the built environment are important determinants of health (Cooper et al., 2008). In addition, seeing nature, having access to green space, and taking part in activities such as community gardens are generally beneficial for mental health across all age groups. Thus, planting trees in urban areas, making sure that there are parks, and maintaining lawns all have the potential to improve mental well-being, decrease stress, and increase effective management of major life issues.

Studies report that children exposed to nature and green space have improved ability to learn, better memory, and better attention (Cooper et al., 2008). At a community level, green space is associated with higher levels of perceived social connectedness to the community and decreased levels of violence (Cooper et al., 2008).

Although there may be beneficial effects from contact with nature, on a global basis, people are increasingly moving to cities. According to the most recent version of the United Nation's World Urbanization Prospects study, "over half of the world's population (54%) lives in urban areas." This figure is expected to increase to 67% in 2050, based on an estimated increase in world population to 9.3 billion (rev.; United Nations, 2014). Because of this trend, work on psychosis has focused mainly on the impact of urban living rather than on the possible benefit of exposure to green spaces.

Cities: A major branch of investigation into the social etiology of psychotic illness began in 1939 with Faris and Dunham's work on the urban environment. Since then, researchers have been investigating the link between living in a city and the risk of schizophrenia. There is evidence that the larger the urban environment the higher the risk of schizophrenia and other psychoses. Initial studies argued that this was because of a drift into cities of people who were more at risk of developing schizophrenia. That does happen, but even when that is accounted for there remains an increased risk of schizophrenia in those who are born or brought up in a city. The longer you live in the city, the higher the risk. The exact reasons for this are unknown. There has not been good work that has been able to disaggregate what the impacts of the city may be. But the city, whatever that may be, is the biggest risk factor for schizophrenia and other psychoses at a population level (Boydell and McKenzie, 2008).

Living in an urban environment is associated with a number of different types of exposures, including the fragmentation of community bonds and economic disparities. Allardyce et al. (2005) found that, after adjusting for social fragmentation and deprivation, there was only a nonsignificant trend toward an association between urbanicity and schizophrenia. Other factors may be important for the association between place and psychosis. For instance, Silver et al. (2002) documented that the proportion of people moving in and out of an area is associated with higher rates of schizophrenia.

Another pilot study reported that increased social cohesion and social efficacy in areas in London were associated with a reduced incidence of psychosis (Boydell et al., 2001); and after controlling for individual deprivation, Boydell et al. (2004) found the rate of schizophrenia correlated with increasing neighborhood inequality, but only in more deprived areas.

Many of the benefits of social bonds and community relations have been captured in the notion of "social capital," which is associated with better mental health (McKenzie and Harpham, 2006). In a study with data from the United Kingdom, Kirkbride et al. (2007) used multilevel Poisson regression to model the simultaneous effects of individual- and neighborhood-level factors. They found that 23% of the incidence of schizophrenia could be attributed to neighborhood-level social risk factors, including socioeconomic deprivation, voter turnout (a proxy for social capital), ethnic fragmentation (proxy for segregation), and ethnic density (95% confidence interval 9.9–42.2). One percent increases in voter turnout and ethnic segregation were both independently associated with a reduced incidence of schizophrenia of 5%, independent of age, sex, ethnicity, deprivation, and population density (Kirkbride et al., 2007). Of course, there are a number of different mechanisms through which such social ecological factors could have their impact on psychosis. Stress may be just one of a number of mediators (Susser et al., 2008).

The neural processes that could mediate the association between urban environments and mental illness have only recently begun to be documented. Increased levels of stress linked to urban residence are considered important, as are models of psychological appraisal and neurocognitive development. There is some evidence that urban upbringing and city living change social evaluative stress processing in humans.

Those who live in a city have increased amygdala activity, and being brought up in a city affects the perigenual anterior cingulate cortex, a key region for regulation of negative affect and stress. Because different parts of the social brain may have different critical developmental periods and social impacts may exert their effects at different times, research findings indicate that brain regions differ in their vulnerability and reactions to city living across the lifespan (Lederbogen et al., 2011; Meyer-Lindenberg, 2010).

Childhood adversity: Childhood social adversity is linked to increased rates of schizophrenia in adult life. The more social adversity present, the higher the risk of developing schizophrenia. Social adversity has been measured in a variety of ways, from bullying and other forms of psychological trauma to material deprivation. Separation from one or both parents for more than a year before the age of 15 has been found to be a powerful risk factor. This is again thought in part to be linked to increased rates of stress.

Immigrant groups: Groups who are under stress have been demonstrated to be particularly at risk. Studies of immigrant groups have reported increased risks of psychosis. Immigration doubles the risk of psychosis in first-generation migrants, and the risk increases in second-generation migrants. Migrants who come from countries where the population is predominantly black and go to a country that is predominantly white have a fourfold increase in risk. However, a study in Ontario was able to compare rates of new psychosis in a variety of immigrant groups. It found that there was significant variability in the risk of developing psychosis for different ethnic groups, with East Asian origin groups having lower rates of psychosis and those of Caribbean origin having higher rates of psychosis. Refugee groups had higher rates of psychosis, irrespective of their place of origin.

Some have argued that a specific possible cause for the differences in rates is the impact of racism on different communities. At an individual level, perceived racism has been linked to increased risk of schizophrenia. Racism has its impact on health through stress but also through behaviors or lifestyles that have an impact on health such as diet and substance use, as well as needing to work two jobs or taking risks to try to improve one's socioeconomic security. Others have argued that social stress through being a minority group thwarted aspirations of the group, or pre-migration trauma or post-immigration problems could be to blame.

Whatever the cause of stress, the bottom-line is that studies report that cumulative exposure to traumatic life events, or the number of life events experienced, is associated with an increased risk for psychosis (van Os et al., 2009), and the British National Psychiatric Morbidity Survey has reported that adverse life events are associated with subsequent psychotic experiences in the general population (Johns et al., 2004). In addition to traumatic major life events, the accumulation of minor events or "daily hassles" has also been linked to psychotic illness (Myin-Germeys and van Os, 2007). But it is not just the number of life events that is important. A life event such as bullying in childhood could lead to a chain of events because of reactions to that or changes in school or changes in self-esteem, which increase the chance of other stress-inducing environmental risk factors associated with psychosis.

The social model of causation argues that schizophrenia is the result of trauma or stress. The more social stress, the more impacts on neurotransmitter mechanisms, the higher is the risk. But in response to social adversity, there are often psychological processes that are triggered, either to decrease and normalize the perception of stress or to make sense of it. Others suggest that stress may be linked to psychosis not through biological mechanisms but through psychological ones.

Psychological Risks and Models

A more psychological model argues that adversity may lead to negative self-esteem or an increased chance that you will blame others for your situation. Being able to appraise situations and having a number of different ways of considering and understanding what is happening help people to feel in control. Children develop social maps through interactions with their parents initially and then with others. Children in houses that are under strain may have less face-to-face time and may on average have fewer schema to help make decisions. Research shows that they may be less able to understand other people's intensions and to understand their agency. Partly because of this, social interactions provoke anxiety. Avoidance of anxiety-provoking situations in childhood can mean that the psychological mechanisms that are needed to deal with ambiguity are not well developed. When stress arises, the triggered coping style is more likely to be social withdrawal and suspicion of the actions of others. This increases the risk of developing paranoid ideation.

Literature outlining the association between childhood trauma and psychosis describes both psychological and neurobiological mechanisms, linking adverse experiences

to psychosis (vanWinkel et al., 2013). These processes have neural correlates: sensitization of the mesolimbic dopamine system, which produces a heightened response to low-level stressors; changes in the immune system; and concomitant changes in the size and function of stress-related brain structures, such as the hippocampus and the amygdala.

These mechanisms also interact, as exemplified by the hypothesis that chronic exposure to social defeat may lead to sensitization of the mesolimbic dopaminergic system and increased risk of schizophrenia (Selten and Cantor-Graae, 2005).

According to the hypothesis, social defeat is "the common denominator" for several environmental risk factors, including childhood trauma, urban upbringing, migration, and drug use. Despite the identification of putative neural mechanisms, it appears that the genes under consideration in much of the current research are not specifically involved in the genesis of psychosis, but more generally in regulating mood (eg, the serotonin transporter gene), neuroplasticity (brain-derived neurotrophic factor; BDNF), and the stress-response system (the FKBP5 gene). Moreover, researchers studying families with a strong genetic predisposition for schizophrenia have found that a cumulative adversity index—which includes childhood illness, family instability, and cannabis use—is significantly associated with the risk of schizophrenia and that this is independent of genetic risk (Husted et al., 2012). Genetic variants and environmental exposures can also interact in ways that are protective and not just harmful. Instead of focusing on "vulnerability genes" that confer increased risk in the presence of certain environments, therefore, Belsky et al. (2009) call for an appreciation of "plasticity genes" that confer a nuanced differential susceptibility: increased risk in some environments and decreased risk in others.

Physiologically and cognitively, exposure to early developmental stressors (such as childhood trauma) may act by sensitizing people to later adverse events, major or minor. Such exposures may increase the likelihood of adverse events, for instance, by shaping the capacity of individuals to form relationships (Myin-Germeys and van Os, 2008). Alternately, they may interface with a person's attributional style, potentially making them more prone to psychotic thinking (Bentall et al., 1994).

New Thinking and New Science

In industry, trade-offs are considered pivotal moments. The most successful manufacturers see trade-offs as an opportunity for innovation. Some argue that prior to the emergence of the Japanese car industry as a major exporter, world markets were dominated by a dichotomous model. The choice for many consumers was between high cost, reliable cars and low cost, less reliable cars. The industry trade-off was cost versus reliability. With significant investment in technology, Japanese car manufacturers were able to side step this trade-off. They were able to produce low-cost reliable cars. This gave them an entry into the market, and their superior fuel efficiency meant that they became more popular during the 1970s oil embargo. They now dominate the market.

Trade-offs are an opportunity for ingenuity and progress. The spurious trade-off between biological or social as the "cause" of schizophrenia can be seen as an opportunity for improvement in our science and our thinking about etiology. Researchers have already started to think differently and to move outside their specific field of exploration.

Social researchers are explaining their results using biological concepts, and biological researchers are trying to develop models of etiology based on their understanding of social and environmental risks.

A variety of findings in both the social and biological literature demonstrate that the two are linked and that maintaining a dichotomy between the two is increasingly difficult.

For instance, it is clear that the urban environment changes the exposure that a person or group has to biological risk factors. For example, there is some work that suggests that malnutrition in utero is linked to increased risk of psychosis in later life. Rates of malnutrition are increased in urban settings. Similarly, in many countries, access to and use of cannabis is linked to place of residence.

More fundamental interactions between biological, environmental, and social are found in the links between genetic predisposition and risk of illness. The vulnerability to developing schizophrenia in people with family members with the illness is influenced by urban residence. The increased risk of schizophrenia linked to being born or brought up in a city is mainly because of increased rates of schizophrenia in those who have familial risk. Studies have shown that the impact of urbanicity of psychotic symptoms is significantly greater in those who have a family history of psychosis, and the impact of cities on rates and risk in this groups is increasing.

Genetic risk also potentiates other biological risks. When people are given the active ingredient in cannabis, some develop psychotic symptoms, but most do not. The group that develop psychotic symptoms are overwhelmingly people with a family history of psychosis. Similarly, imaging studies have reported that the active ingredient in cannabis can have a direct toxic effect on the brain, leading to decreased brain volume. However, this toxic effect is only seen in people with a family history of schizophrenia. It is not seen in those without a family history (van Os et al., 2010).

Social factors also interact with each other. Social cohesion is linked to the rate of schizophrenia in an area.

However, the impact of social cohesion on schizophrenia risk is only present on ethnic minority groups and those from lower socioeconomic groups.

These and other findings argue that the different risk factors may potentiate or decrease the impact of each other on overall risk. Different types of risk factors may interact, and the actions of specific risk factors to increase the rates of illness may be dependent on other risk factors being present.

There is a complex web of causation, but there are different sciences at different levels, individual and ecological, involved. Moreover, both the biological literature (cannabis and seasonality), the psychological literature (development of concepts of self and schema), and the social (childhood social adversity) all point to the action of specific risk factors being exquisitely linked to specific time periods when the brain is maturing.

However, there is one factor that has been missing and ushers in a new way of thinking. This is social context. Distress or problems with functioning, which are important facets of psychiatric diagnoses, are context related. They speak to an individual's interaction with society, their reflection of their own being, and their interaction with the environment.

To understand psychosis, it is important to understand these interactions.

One way of thinking about mental illness is that it can be considered a reflection of the biological and psychological mechanisms we use to adapt to the environment. The symptoms that we see and the behaviors or thoughts are the person trying to rise to challenges that are faced.

The psychological and social schema that we build to help us understand the world are there to maximize our ability to live in such a complex environment. Like our stress response, these are adaptive mechanisms. Our response to social difficulties, life events, or everyday hassles is to use our psychological and social resources to be able better to understand the situation, predict what is going to happen, and be in control. We adapt our actions and thoughts based on our schema, so we minimize the risk to ourselves and maximize the benefit.

If our schema are in line with others, our adaptations to life's challenges are considered reasonable. If they are considered logical but unlawful, they are dealt with legally. But if they are considered illogical, they may be dealt with by mental health professionals. In discussion with people with psychosis, there is usually a reason for their actions. They are usually dealing with stressful situations or battling personal psychological issues that require action to decrease anxiety.

Whether these adaptations are considered illnesses or not depends on the differential acceptance by society to specific types of behaviors and thoughts. For instance, if you hear the voice of God in a charismatic church when you are looking to decrease your stress through worship of a higher being, that is not considered a symptom. But if you hear the voice of God while sitting in your office, and act on it, your coworkers may be troubled by it.

Context is enshrined in diagnoses and the building blocks of diagnosis, psychiatric symptoms. Diagnoses change over time. The ICD, DSM, and Chinese systems evolve with the social context, and when they are too far out of step with social norms, they tend to modify themselves. A recent debate has been about the changes in the diagnosis of depression during grief. Thirty years ago psychiatrists only diagnosed depression during a period of grief after 6 months. Depression before this time was considered a normal part of the process. Two decades ago, guidance changed, and if the symptoms were serious, enough depression was diagnosed after 2 months. In DSM5, the diagnosis of depression is possible 2 weeks into a period of grief (APA, 2013).

Though there has been some consternation about this, and about what this means for us as a human race, pragmatists argue that people are expected to function 2 weeks after they have lost a loved one, and that most people can (McKenzie, 2013). Allowing psychiatrists to diagnoses and treat depression in the minority of people who are severely affected and cannot function 2 weeks after a bereavement aligns with societal expectations in some high-income countries. This would of course be viewed with horror by other cultures where there are clear expectations for defined periods of grief for relatives, almost all of which last longer than 2 weeks.

Similarly, with regard to symptoms, the definition of a delusion is not simply that a person has an unshakable thought that is not based on fact and is erroneous, but the thought needs to be outside the realm of normality for a person's social circle.

Our psychology is in a constant state of adaptation. Through the stress mechanism and through other neurotransmitter systems such as dopamine, our physiology is also adapting to maximize our ability to live in society.

However, there is a further complication; from a biological perspective, the brain helps us adapt to the environment, but it also develops in response to the environment. Some environmental factors promote healthy brain development, and some impede it, but many have a variable impact depending on context. Whether environmental events contribute to individual vulnerability or resiliency depends on many factors, including the previous history of environmental exposures. Individuals who have been exposed to more positive environmental influences, that is, fewer social risk factors, tend to be more resilient. For these individuals, exposure to indeterminate social factors leads to the development of a more resilient coping style, and they are more likely to be able to meet new challenges. However, if a person has been exposed to more

social risk factors for mental illness, some environmental factors are more likely to be experienced as burdensome, and this may further undermine the development of resilience.

These processes have neurodevelopmental parallels: both the structure and function of the brain are linked to environmental influences. van Os et al. (2010) have detailed the development of brain architecture, as well as neurocognition, affected regulation, and social cognition throughout childhood. They reviewed the associations between specific factors in the social environment and neurocognitive development and linked problems in neurocognitive development during childhood to a later increased risk of schizophrenia (van Os et al., 2010).

If mental illnesses are disorders of adaptation, and the way the brain adapts is in part a response to social and environmental contexts, then mental illness lies in the interaction between brain and environment. The brain is married to the environment, and it is in that relationship that we see mental illnesses. Trying to understand the marriage by looking at only one partner is unlikely to give an accurate picture. Investigating one without the other resembles attempts to understand and repair a marriage without both parties present. It may give a distorted view of what is happening and may not offer the best basis for treatment.

This leads to a movement away from research that focuses entirely on biology or social factors toward investigations that focus on the interactions between the two, as well as the mechanisms underlying those interactions, and it is a crucial development in the field (van Os et al., 2010).

From this, it follows that we are less likely to find the causes of mental illness in the brain or in the social environment. We are more likely to find causes in the processes through which the brain adapts to the environment.

These processes can be considered not only at an individual level but also at ecological and interactional levels. Because they are adaptations, we should consider them over time, but we should also consider how the ability to adapt may change over time.

Part of the new thinking of the causes of schizophrenia and other psychoses is to move toward investigation of neurogenesis, epigenetics, and inflammation. These are all dynamic ways in which the brain adapts itself to optimize the way the body reacts to the environment.

Neurogenesis is the study of growth of nerve cells. There is a growing literature on the possibility of stimulating growth in the hippocampus and other brain areas that are affected by schizophrenia and other psychoses. Less work to date has attempted to consider why there is cell death and how to stop it. The concept is a revolution in genetics. Scientists have found that genes can be turned on and off, and they may or may not express themselves depending on environmental and other stimuli. Rather than natural selection slowly altering the gene pool, epigenetic effects can be quick and can be inherited. If schizophrenia is in part due to new gene expression, these new expressions may be genes being turned on an off rather than new mutations. Understanding how to turn genes off in response to triggers or understanding how to modulate the triggers may help to decrease the risk of psychosis.

Inflammation is the body's way of dealing with unwanted invasion, whether this is due to internal processes gone wrong or external such as infections. Inflammatory processes have been identified in many major mental illnesses, including schizophrenia, and further understanding of why these happen and what they mean is underway.

At the level of gene−environment interaction, it has been suggested that even minor life events and daily hassles interact with polymorphisms known to be involved in dopamine neurotransmission to cause differential stress reactivity and psychotic experiences (van Winkel et al., 2008). Of note, the same polymorphism has been shown to correlate with differential risk for psychosis in individuals who use cannabis (Caspi et al., 2005), further highlighting the complex interplay between multiple biological and environmental risk factors. Similarly, at a structural level, neuroplasticity may be important.

From Complexity to Utility

Using these understandings to produce interventions is still some way off. Though, self-regulation of adaptation through learning and other psychological processes is increasingly being seen as a possible promising avenue for the treatment, if not the cure of some of the symptoms of schizophrenia; at a policy and ecological level, the organization of our interpersonal safety net in response to the threat that make us stressed and the way we develop our communities and cities is likely to be a vital route to prevention.

There is clearly now a deeper understanding of the etiology of schizophrenia and other psychoses than there was previously.

I will use the four dimensions model of causation to summarize our current understanding. I use this in part because it mixes biological, social, and psychological mechanisms at an individual level and also similar mechanisms at the ecological level. In addition to identifying interactions between individual and ecological levels, it also recognizes interactions between risk factors within the different levels.

At an individual level, our understanding is similar to that of heart disease in that there is an inherited risk, but whether one develops a heart attack or not depends on other risk, protective, and health-promoting factors that are encountered.

The risk of developing a psychosis for any individual depends on inherited vulnerabilities, but in addition, it rests on the balance of exposures to factors that either increase risk for illness or enhance mental health.

This chapter has detailed the genetic and other biological risk factors for schizophrenia and other psychoses. Social risk factors could include the use of certain drugs (especially cannabis), racial discrimination, and childhood experiences influencing development, such as bullying and psychological trauma, separation from parents, and other childhood adversities (Boydell et al., 2004).

The number and severity of exposures as well as their interactions may all contribute to the risk of developing a psychotic illness. Previous work has shown that the greater the number of risk factors, the higher the risk of psychosis. Unfortunately, there has been less work on protective factors than risk factors.

At the ecological level, societal factors may change the amount and type of environmental exposures that a group are exposed to. Though this means it may change the risk profile for a whole population or increase the vulnerability of specific socially demarcated groups.

The model here is similar to that of diabetes, where changes in the availability and quality of certain types of food and cultural changes in activity with increasingly sedentary lifestyles have led to markedly increased rates of the illness.

Groups with similar individual-level risk profiles may have different rates of illness dependent on the ecological environment. In addition to factors like diet and exposure to infectious diseases that influence early neurodevelopment, environmental risk factors that may contribute to the risk of psychosis include city birth and city living, social cohesion, social fragmentation, being a member of a minority group living in areas with low population densities of one's group, and migrants from countries that are predominantly black living in countries that are predominantly white.

Of course, individual and ecological risks interact. For example ecological factors may decrease the rates of illness by decreasing the impact of individual risk factors. The social safety net, for instance, may decrease the impact of certain life events on the risk for increasing the rate of schizophrenia at a population level. Whereas, other ecological factors could interact with individual-level factors to increase risk. Social disorganization may decrease the capacity to cope with social risk factors such as family discord or unemployment. There is some evidence that the impact of minority group membership on psychosis risk is linked to the density of that minority group in a geographic region or neighborhood. The incidence of schizophrenia in minority groups is higher in those who live in areas where there are fewer other people from minority groups. On the other hand, institutional racism is likely to increase the impact of individual level racism on mental illness.

Individual and ecological factors may not simply be independent variables acting in concert, but they may interact in ways that amplify or dampen each other's effects. A further example would be cannabis use, and this demonstrates how interactions can produce a chain of events.

Cannabis use may increase a person's risk of developing a psychotic illness. At an ecological level, the availability of cannabis in the community could increase the risk of cannabis use in the first place. Moreover, depending on social context, regular cannabis use may offer access to a subculture, or a different environment, characterized by an increase in daily hassles and life events, which increases the risk of exposure to other social factors associated with psychosis. Exposure to more life events and daily hassles may lead to higher levels of perceived stress and thereby increase cannabis use, thus further increasing the risk of psychosis. The link between individual and ecological processes in this example may trigger a chain of events resulting in further interactions among social risk factors.

Social factors also may alter biological risk in multiple ways. For example, sociocultural factors at an ecological level, such as the trend toward older paternal age at conception, may change psychosis risk in offspring at a population level by increasing the rate of children with genetic vulnerability (March and Susser, 2006). New evidence is rapidly emerging in this field. Binbay et al. (2012), for instance, have reported that the association between familial liability to severe mental illness and the expression of illnesses within the psychotic spectrum is stronger in more deprived neighborhoods, in high unemployment neighborhoods, and in neighborhoods high in social control.

Further complexity is introduced by work on child brain development. This work has shown that the same exposure to an individual-level social determinant may have negative or positive impacts on the developing brain depending on the individual's previous history of exposure to social determinants. If the balance of exposures has been negative, then an otherwise neutral factor may be experienced as negative. Alternatively, if the balance of exposures has been positive, some challenges may actually enhance brain development (Knudsen et al., 2006). Through this means, context may actually change the nature of an exposure from positive to negative.

This also underlines the importance of "time," an individual's history and the possibility that the sequence of exposure may be important.

Time is important in several other ways. First, sufficient exposure to an individual-level or ecological risk factor may only occur over time. Second, time may be needed for the interaction between individual and ecological risk factors to amplify. Third, there are sensitive periods in brain

development during which exposure to certain risk factors may be more important.

For instance, being born and brought up in a city is etiologically more significant in schizophrenia than living in a city per se (Lederbogenet et al., 2013; Marcelis et al., 1999; Pedersen and Mortensen, 2001). Other risk factors such as separation from parents may be more important in childhood than adult life. Fourth, there may be a delay in time between the exposure to a risk factor and the development of psychosis. For instance, the impact of maternal malnutrition on psychosis risk may only be evident when offspring reach early adulthood (Susser et al., 2008). Last, the impact that a social factor has on an individual may be determined in part by the cumulative or profound effect of previous life experiences. These include the history of prior exposures linked to sensitization or resilience and the way that history may change our perception of our environment. A 10-year follow-up study on a population sample of 3021 people in Germany recently reported that early adversity may impact later expression of psychosis by increasing exposure to later adversity and/or by rendering individuals more sensitive to later adversity if these early experiences are severe (Lataster et al., 2012).

That there are mechanisms at an individual level such as neurogenesis, inflammation, and epigenetics that offer plausible explanations for how the social world gets under the skin to cause schizophrenia and other psychoses is exciting. Similarly, the psychological mechanisms for the production of psychosis offer avenues for treatment.

However, psychosis can ruin individuals and families. Acute psychosis is a dangerous condition that may lead to suicide and certainly can scar an individual's life and that of their family and friends. Minimizing the impact through effective treatment is one goal, but prevention is the one that I find more attractive.

Using our models of causation, we can think through possible intervention not just at the individual level but also at the ecological and interactive levels. For example, we could use it to estimate whether decreasing access to cannabis, decriminalizing it so that we de-link use from social harm, or whether we push hard for use after the age of 18 would be the most efficient for protecting the public. We can investigate whether population-based measures would be best or whether we should target specific groups, such as those with a family history of psychosis. We may want to investigate the links between the urban environment, the urban brain, and the risk of psychosis. Understanding how our environment programs our brain may be an important and vital area of research in the future, especially with the rise of the mega city in China, India, and Central and South America. We are set to transcend the nature or nurture debate with our understanding that for psychosis nature is nurture, and our minds are a reflection of our adaptation to our environment.

These are exciting but early days in etiological research into psychosis based on a multilevel understanding. We have not resolved the difficulty that schizophrenia and other psychoses are syndromes rather than specific illnesses, and so there may be many causes. But I believe that trying to understand the multiple possible pathways through which these psychoses are produced and allowing for a variety in mechanisms is useful. In some ways, it forces us to consider what etiology is rather than focusing on the etiology of what.

I believe the tension between the biological and the social led to a trade-off that has sparked ingenuity. Whether we use this to move to another level has yet to be seen, but all the elements are there for a revolution in our understanding of mental illness based on the work on the etiology of psychosis.

REFERENCES

Allardyce, J., et al., 2005. Social fragmentation, deprivation and urbanicity: relation to first-admission rates for psychoses. British Journal of Psychiatry 187, 401–406.

American Psychiatric Association, 2015. Diagnostic and Statistical Manual of Mental Disorders, fifth ed. American Psychiatric Association, Arlington, USA.

Andréasson, S., Allebeck, P., Engström, A., Rydberg, U., December 26, 1987. Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. Lancet 2 (8574), 1483–1486.

Belsky, J., et al., 2009. Vulnerability genes or plasticity genes? Molecular Psychiatry 14, 746–754.

Bentall, R.P., Kinderman, P., Kaney, S., 1994. The self, attributional processes and abnormal beliefs: towards a model of persecutory delusions. Behaviour Research and Therapy 32 (3), 331–341.

Binbay, T., Drukker, M., Alptekin, K., et al., December 2012. Evidence that the wider social environment moderates the association between familial liability and psychosis spectrum outcome. Psychological Medicine 42 (12), 2499–2510. http://dx.doi.org/10.1017/S0033291712000700.

Boydell, J., et al., 2001. Incidence of schizophrenia in ethnic minorities in London: ecological study into interactions with environment. BMJ 323 (7325), 1336–1338.

Boydell, J., et al., 2004. The association of inequality with the incidence of schizophrenia–an ecological study. Social Psychiatry and Psychiatric Epidemiology 39 (8), 597–599.

Boydell, J., McKenzie, K., 2008. Society, place and space. In: Morgan, C., McKenzie, K., Fearon, P. (Eds.), Society and Psychosis. Cambridge University Press, Cambridge, pp. 77–94.

Caspi, A., et al., 2005. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. Biological Psychiatry 57 (10), 1117–1127.

Cooper, R., Boyko, C., Codinhoto, R., 2008. State-of-science review: SR-DR2 the effect of the physical environment on mental wellbeing. In:

Mental Capital and Well Being: Making the Most of Ourselves in the 21st Century. HaCIRIC/University of Salford. http://www.bis.gov.uk/assets/foresight/docs/mental-capital/sr-dr2_mcw.pdf.

Di Forti, M., Morgan, C., Dazzan, P., et al., November 2009. High-potency cannabis and the risk of psychosis. British Journal of Psychiatry 195 (6), 488–491. http://dx.doi.org/10.1192/bjp.bp.109.064220.

Faris, R., Dunham, H., 1939. Mental Disorders in Urban Areas. University of Chicago Press, Chicago, p. 3535.

Fusar-Poli, P., et al., 2007. Neurofunctional correlates of vulnerability to psychosis: a systematic review and meta-analysis. Neuroscience & Biobehavioral Reviews 31 (4), 465–484.

Hosman, C., Jane Llopis, E., 2005. The evidence for effective mental health promotion. In: Herman, H., Saxzena, S., Moodie, R. (Eds.), Promoting Mental Health, Concepts, Emerging Evidence, Practice. Geneva World Health organization, pp. 169–188.

Husted, J.A., Ahmed, R., Chow, E.W., Brzustowicz, L.M., Bassett, A.S., May 2012. Early environmental exposures influence schizophrenia expression even in the presence of strong genetic predisposition. Schizophrenia Research 137 (1–3), 166–168. http://dx.doi.org/10.1016/j.schres.2012.02.009. Epub 2012 Mar 3.

Insel, T., 2015. http://blogs.scientificamerican.com/mind-guest-blog/rethinking-how-we-diagnose-psychosis/.

Johns, L.C., et al., 2004. Prevalence and correlates of self-reported psychotic symptoms in the British population. British Journal of Psychiatry 185, 298–305.

Jones, S.R., Fernyhough, C., 2007. A new look at the neural diathesis–stress model of schizophrenia: the primacy of social-evaluative and uncontrollable situations. Schizophrenia Bulletin 33 (5), 1171–1177.

Kirkbride, J.B., Boydell, K., Ploubidis, G.B., Morgan, C., Dazzan, P., McKenzie, K, Murray, R.M., 2007. Testing the association between the incidence of schizophrenia and social capital in an urban area (PDF Download Available). Psychological Medicine, Page 1 of 12. http://dx.doi.org/10.1017/S0033291707002085.

Knudsen, E.I., Heckman, J.J., Cameron, J.L., Schonkoff, J.P., 2006. Economic, neurobiological and behavioural perspectives on building Americas future workforce. www.pnas.org/cgi/doi/10.1073/pnas0600888103.

Lataster, J., Myin-Germeys, I., Lieb, R., Wittchen, H.U., van Os, J., May 2012. Adversity and psychosis: a 10-year prospective study investigating synergism between early and recent adversity in psychosis. Acta Psychiatrica Scandinavica 125 (5), 388–399. http://dx.doi.org/10.1111/j.1600-0447.2011.01805.x. Epub 2011 Nov 30.

Lederbogen, F., Kirsch, P., et al., 2011. City living and urban upbringing affect neural social stress processing in humans. Nature 474 (7352), 498–501.

Lederbogen, F., Haddad, L., Meyer-Lindenberg, A., December 2013. Urban social stress – risk factor for mental disorders. The case of schizophrenia. Environmental Pollution 183, 2–6. http://dx.doi.org/10.1016/j.envpol.2013.05.046.

March, D., Susser, E., 2006. Invited commentary: taking the search for causes of schizophrenia to a different level. American Journal of Epidemiology 163 (11), 979–981.

Mausner, J.S., Kramer, S., 1985. Mausner & Bahn Epidemiology: An Introductory Text. W.B. Saunders Company, Philadelphia.

Marcelis, M., Takei, N., van Os, J., 1999. Urbanization and risk for schizophrenia: does the effect operate before or around the time of illness onset? Psychological Medicine 29 (5), 1197–1203.

McGrath, J., Saha, S., Chant, D., Welham, J., 2008. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiologic Reviews 30, 67–76. http://dx.doi.org/10.1093/epirev/mxn001.

McKenzie, K., 2013. Mind Games the Walrus. http://thewalrus.ca/mind-games/.

Mckenzie, K., Harpham, T., 2006. Social Capital and Mental Illness. Jessica Kinglsey Publications, London, UK.

Morgan, C., McKenzie, K., Fearon, P., 2008. Society and Psychosis. Cambridge University press, London, England.

Meyer-Lindenberg, A., November 11, 2010. From maps to mechanisms through neuroimaging of schizophrenia. Nature 468 (7321), 194–202. http://dx.doi.org/10.1038/nature09569.

Myin-Germeys, I., van Os, J., 2007. Stress-reactivity in psychosis: evidence for an affective pathway to psychosis. Clinical Psychology Review 27 (4), 409–424.

Myin-Germeys, I., van Os, J., 2008. Adult adversity: do early environment and genotype create lasting vulnerabilities for adult social adversity in psychosis? In: Morgan, C., McKenzie, K., Fearon, P. (Eds.), Society and Psychosis. Cambridge University Press, Cambridge, pp. 127–142.

Nuechterlein, K.H., Dawson, M.E., 1984. A heuristic vulnerability/stress model of schizophrenic episodes. Schizophrenia Bulletin 10 (2), 300–312.

van Os, J., Kenis, G., Rutten, B., 2009. Schizophrenia and the environment. Nature 468, 203–212, 2010.

van Os, J., Kenis, G., Rutten, B.P., 2010. The environment and schizophrenia. Nature 468 (7321), 203–212. http://dx.doi.org/10.1038/nature09563.

van Os, J., Kapur, S., 2009. Schizophrenia. Lancet 374 (9690), 635–645, 22.

Pedersen, C.B., Mortensen, P.B., November 2001. Evidence of a dose-response relationship between urbanicity during upbringing and schizophrenia risk. Archives of General Psychiatry 58 (11), 1039–1046.

Phelan, J.C., Link, B.G., Tehranifar, P., 2010. Social conditions as fundamental causes of health inequalities: theory, evidence, and policy implications. Journal of Health and Social Behavior 51, S28–S40.

Sartorius, N., Shapiro, R., Jablensky, A., 1974. The international pilot study of schizophrenia. Schizophrenia Bulletin 1 (11), 21–34. http://dx.doi.org/10.1093/schbul/1.11.2.

Selten, J.P., Cantor-Graae, E., 2005. Social defeat: risk factor for schizophrenia? British Journal of Psychiatry 187, 101–102.

Shah, J., Mizrahi, R., McKenzie, K., July 2011. The Four dimensions model for the social aetiology of psychosis. British Journal of Psychiatry 199 (1), 11–14.

Silver, E., Mulvey, E., Swanson, J., 2002. Neighbourhood structural characteristics and mental disorder: Faris and Dunham revisited. Social Science & Medicine 55 (8), 1457–1470.

Susser, E., St Calir, D., He, L., 2008. Latent effects of prenatal malnutrition on adult health the example of schizophrenia. Annals of the New York Academy of Sciences 1136, 185–192.

Susser, M., Susser, E., 1996a. Choosing a future for epidemiology: I. Eras and paradigms. American Journal of Public Health 86 (5), 668–673.

Susser, M., Susser, E., 1996b. Choosing a future for epidemiology: II. From Black Box to Chinese Boxes and eco- epidemiology. American Journal of Public Health 86 (5), 674–677.

van Winkel, R., van Nierop, M., Myin-Germeys, I., van Os, J., January 2013. Childhood trauma as a cause of psychosis: linking genes,

psychology, and biology. Canadian Journal of Psychiatry 58 (1), 44–51.
van Winkel, R., et al., 2008. Evidence that the COMT(Val158Met) polymorphism moderates sensitivity to stress in psychosis: an experience-sampling study. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics 147B (1), 10–17.
Walker, E., Mittal, V., Tessner, K., 2008. Stress and the hypothalamic pituitary adrenal axis in the developmental course of schizophrenia. Annual Review of Clinical Psychology 4, 189–216.
World Health Organization, 2015. International Classification of Disease. http://www.who.int/classifications/icd/en/.

FURTHER READING

Brenner, N., Schmid, C., 2015. Towards a new epistemology of the urban? City 19 (2–3), 151–182.
Canguilhem, G., 2008 [1965]. Knowledge and Life. Fordham University Press, New York.
Caspi, A., McClay, J., et al., 2002. Role of genotype in the cycle of violence in maltreated children. Science 297 (5582), 851–854.
Caspi, A., Moffitt, T.E., 2006. Gene–environment interactions in psychiatry: joining forces with neuroscience. Nature Reviews Neuroscience 7, 583–590.
Galea, S., Uddin, M., et al., 2011. The urban environment and mental disorders. Epigenetics 6 (4), 400–404.
Geuze, E., Vermetten, E., Bremner, J.D., 2005. MR-based in vivo hippocampal volumetrics: 2. Findings in neuropsychiatric disorders. Molecular Psychiatry 10 (2), 160–184.
Goldmann, E., Aiello, A., et al., 2011. Pervasive exposure to violence and posttraumatic stress disorder in a predominantly African American urban community: the detroit neighborhood health study. Journal of Traumatic Stress 24 (6), 747–751.
Gould, E., Reeves, A.J., et al., 1999. Neurogenesis in the neocortex of adult primates. Science 286 (5439), 548–552.
Kelly, B.D., O'Callaghan, E., Waddington, J.L., Feeney, L., Browne, S., Scully, P.J., Clarke, M., Quinn, J.F., McTigue, O., Morgan, M.G., Kinsella, A., Larkin, C., January 2010. Schizophrenia and the city: a review of literature and prospective study of psychosis and urbanicity in Ireland. Schizophrenia Research 116 (1), 75–89. http://dx.doi.org/10.1016/j.schres.2009.10.015.
Kirkbride, J.B., 2014. Hitting the floor: understanding migration patterns following the first episode of psychosis. Health & Place 28 (0), 150–152.
Kirkbride, J.B., Boydell, J., et al., 2008. Testing the association between the incidence of schizophrenia and social capital in an urban area. Psychological Medicine 38 (08), 1083–1094.
Landecker, H., Panofsky, A., 2013. From social structure to gene regulation, and back: a critical introduction to environmental epigenetics for sociology. Annual Review of Sociology 39 (1), 333–357.
Lieberman, J., et al., 2001. Longitudinal study of brain morphology in first episode schizophrenia. Biological Psychiatry 49 (6), 487–499.
Leuner, B., Glasper, E.R., et al., 2010. Parenting and plasticity. Trends in Neurosciences 33 (10), 465–473.
Mason, O., et al., 2004. Risk factors for transition to first episode psychosis among individuals with 'at-risk mental states'. Schizophr. Res. 71 (2–3), 227–237.
March, D., Hatch, S.L., et al., 2008a. Psychosis and place. Epidemiologic Reviews 30 (1), 84–100.
March, D., et al., 2008b. Conceptualising the social world. In: Morgan, C., McKenzie, K., Fearon, P. (Eds.), Society and Psychosis. Cambridge University Press, Cambridge.
McGowan, P.O., Sasaki, A., et al., 2008. Promoter-wide hypermethylation of the ribosomal RNA gene promoter in the suicide brain. PLoS One 3 (5), e2085.
Mirescu, C., Peters, J.D., et al., 2004. Early life experience alters response of adult neurogenesis to stress. Nature Neuroscience 7 (8), 841–846.
Miller, P., et al., 2001. Genetic liability, illicit drug use, life stress and psychotic symptoms: preliminary findings from the Edinburgh study of people at high risk for schizophrenia. Social Psychiatry and Psychiatric Epidemiology 36 (7), 338–342.
van Os, J., et al., 2001. Prevalence of psychotic disorder and community level of psychotic symptoms: an urban-rural comparison. Archives of General Psychiatry 58 (7), 663–668.
Papadopoulos, D., 2011. The imaginary of plasticity: neural embodiment, epigenetics and ecomorphs. Sociological Review 59 (3), 432–456.
Ryan, M.C., et al., 2004. Evidence of basal pituitary-adrenal overactivity in first episode, drug naive patients with schizophrenia. Psychoneuroendocrinology 29 (8), 1065–1070.
Shevlin, M., et al., 2008. Cumulative traumas and psychosis: an analysis of the national comorbidity survey and the British Psychiatric Morbidity Survey. Schizophrenia Bulletin 34 (1), 193–199.
Spauwen, J., van Os, J., 2006. The psychosis proneness: psychosis persistence model as an explanation for the association between urbanicity and psychosis. Epidemiologia e Psichiatria Sociale 15 (4), 252–257.
Soares, J.C., Innis, R.B., 1999. Neurochemical brain imaging investigations of schizophrenia. Biological Psychiatry 46 (5), 600–615.
Walker, E.F., Diforio, D., 1997. Schizophrenia: a neural diathesis-stress model. Psychological Review 104 (4), 667–685.

Chapter 27

The Flexible Psychological Concept of Normality

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Our reality engine constructs everything we see.

Donald Hoffman

Our earliest attempts to unpack evolutionary theory for humanity framed some of our earliest conceptions of psychological normality. Unfortunately, but unavoidably it seems, such attempts too were responsible for fueling our pursuit of and fear of psychological abnormality. While a language and *science* of abnormality reigned and while normality existed unchallenged and uncontested in the background, our repeated attempts to contain psychological abnormality, to classify it and to dissect it, temporarily moved both constructs beyond our reach. Fortunately, evolutionary theory also however eloquently revealed the adaptive nature of much that we had considered to be psychologically abnormal and reminded us that perceived abnormality may often appear impressively normal when the demands of the environment and our innate adaptive biases are acknowledged.

This chapter considers the flexibility of normality from two very different perspectives. Part one attributes normality's flexibility to a history that reveals how we impulsively and perilously promoted the pursuit of psychological abnormality and obdurately created a disease-based model to account for atypical psychological functioning. The flexibility of normality from this perspective is attributable primarily to our failed and failing attempts to contain abnormality. Specifically, our failure to successfully distinguish between normal psychological functioning and abnormal psychological functioning and our failure to reveal a physiological basis for much that we have judged to be psychologically atypical have continued not only to compound our confusion, but more importantly, have distracted our attention from the evolutionary context of human psychology and the likelihood that "abnormal" may often be something to be valued and protected.

Having considered our recent history with ab/normality, part two considers the construct within a much broader timeline. Normality's flexibility from this perspective is attributable to a perceived reality that is governed by our innate ethnocentrism and most primitive adaptive biases. Ab/normality from this evolutionary perspective is constructed. What we perceive and believe to be ab/normal is informed directly by our reaction and attraction to what is safe, fit, and beneficial and our avoidance of what is harmful, dangerous, or threatening. From this perspective, many experiences that cause suffering, distress, and reduced quality of life need not always indicate pathology or malfunction. Such experiences instead may often be *symptomatic,* not of disease, but of adaptation, defense, and fitness.

While our belief and investment in normality and abnormality has far outweighed our ability to scientifically operationalize either concept, or our ability to empirically distinguish between the two, it is precisely this *blind* investment that may help us to appreciate why ab/normality exists and why we have found it so difficult to contain.

PART ONE

Because of how normality was originally framed, and by whom, our confidence in its existence and our convictions about its discriminatory status were always likely to be somewhat exaggerated and misplaced. The history of our pursuit of normality has revealed much about the concept itself, and it is to this history that we first turn to appreciate how our current models of psychological ab/normality were originally conceived, investigated, and established. From eugenicist confusion in the earliest translations of

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00027-2

Darwinian Theory for humanity to the medicalization of psychological distress by psychiatry and the race to reveal the genetic architecture of the many alleged *diseases* of the mind, normality was quickly relegated to the periphery, while abnormality moved center stage.

A number of esteemed authors have offered detailed and eloquent historical accounts of our precarious pursuit of abnormality and have offered some of the most valuable and insightful chronologies of its evolution as a concept (see Whitaker, 2002; Read et al., 2004; Bentall, 2009; Bartlett, 2011; Frances, 2013; Whitaker and Cosgrove, 2015). Some of the most notable moments and individuals from these historical accounts have been selected here to help capture the genesis of normality and to reveal the beginnings of society's investment in, and fear of, abnormality. While it is acknowledged that moments in history can often be selectively pieced together to manufacture support for a given perspective, the following narrative attempts only to demonstrate that the flexibility of normality, from a psychological standpoint, may be partly attributable to beginnings that favored the identification and measurement of abnormality and that the motivations for doing so may have compromised our attempts to understand these concepts ever since.

Eugenics' Normality

> *Why do we preserve these useless and harmful beings? The abnormal prevent the development of the normal.*
>
> Alexis Carrel

From the outset, our attempts to capture and contain normality were articulated within an evolutionary framework: a survival of the fittest mind-set. Normality it seemed was something to be identified, protected, and incubated: the ultimate strain that needed to be preserved. Ten years after Darwin's *On the Origin of Species*, Francis Galton authored *Hereditary Genius* (1869). Greatly influenced by his cousins' revelations, Galton (Darwin's cousin and one of the first to explore Gaussian distributions of human traits and behaviors in the general population) was determined to reveal evolution's intended road map for humanity. In *Hereditary Genius*, Galton proposed that intelligence and social dominance were heritable traits. Sampling nearly a thousand prominent figures from English high society, Galton concluded that a small number of English families possessed superior "germ plasm" and that this germ plasm was the heritable foundation of their advanced intellect and subsequent status in society.

From the beginning, it seemed normality was explicitly evident in society. It was there for everyone to see. Power, wealth, intellect, and status were the most obvious signs and signals of fitness in Victorian times, and given that these characteristics were identifiable and consistent across generations and within families, society now knew what to invest in to ensure the future success and advancement of the species. Unfortunately, recognizing this fitness was only the beginning. It also needed to be preserved and to do that society needed to ensure that the germ plasm of the *fit* was, at all costs, protected from the *unfit*. Normality it seemed had truly arrived but so too had its greatest threat.

The identification, classification, and segregation of abnormality fast became society's most pressing challenge. Galton's writings (and those of many other eugenicists of the time) were quickly politicized, and European and US ruling classes set about legislating to improve the human stock. Eugenics (meaning "well-born") became the *scientific* justification not only for the classification of the normal ideal but for demarcating the first boundaries between normality and abnormality and importantly for introducing a genetic and physiological basis for its division. From a eugenics perspective the mentally distressed and disabled of society represented the most obvious and most extreme deviation from this normal ideal. Prominent psychiatrists of the time speculatively referred to "degenerate heredity" and "flawed germ plasm" passed from one generation to the next. While the mentally distressed were believed to be the recipients of the most defective germ plasm, inherited gradually over many generations of poor breeding, other groups also clearly exhibited abnormality, simply by virtue of their identity as ethnic, racial, or religious minorities or their status as criminals or social outcasts. Abnormality it seemed was as easily identifiable as normality. These groups, visibly distinct from the *fittest* in society, if permitted, would continue to spread their defective germ plasm. Insanity and poverty quickly approximated low fitness, and existing democratic principles advocating fraternity, equality, and social programs of education and health for all soon it seemed felt the burden of a scientific revolution that could clearly evidence man's costly interference with natural selection.

In the early 1890s, leading eugenicists were calling for the mass sterilization of the insane, poor, criminal, and the *unfit*. It seemed that high society had quickly acquired the capacity for identifying and classifying *fitness* (normality) and that affluence and social status correlated almost perfectly with whatever this classification was. While such proposals were initially only entertained among the scientific community, by 1896 the State of Connecticut in America introduced legislation prohibiting the insane from marrying, and by 1933, marriage prohibition for the insane was enacted across North America. In 1907 the State of Indiana introduced the United States' first sterilization law, justifying it on the basis that heredity had been scientifically evidenced to be central to the transmission of crime, idiocy, and imbecility. Those eligible for sterilization

included criminals, idiots, the feeble-minded, imbeciles, lunatics, drunkards, drug fiends, epileptics, syphilitics, moral and sexual perverts, and those deemed diseased and degenerate (Whitaker, 2002). Europe also followed suit, and in 1933, Ernst Rüdin, who worked at the German Research Institute of Psychiatry, helped to introduce legislation in Germany for the compulsory sterilization of all psychiatric patients. Some seven years later, Germany would begin to *dispose* of abnormality. Inspired by a eugenics-based classification of fitness, approximately 70,000 psychiatric patients across Europe would be gassed during WWII.

The scientific and political elite across Europe and the United States of America it seemed had discovered the boundaries of normality and had underpinned their new discovery with a *robust body of scientific evidence*. Two notable individuals who pioneered the *scientific* demarcation of abnormality and facilitated the enactment of eugenics inspired laws of sterilization are worth noting: Charles Davenport and Aaron Rosanoff. Theirs is a history that exemplifies the ways and means by which we first began to differentiate normal form and function from abnormal and by which we socially, politically, and *scientifically* constructed our normal and abnormal ideals.

Charles Davenport, a Harvard-educated biologist, influenced by Gregor Mendel's revelations about genetic transmission and the dominant and recessive traits of pea plants, decided to demonstrate that human traits were also under the influence of gene expression. Importantly, however, Davenport was an ardent eugenicist and given the scientific and socio-political views of the day biasedly hypothesized that immigrants and social degenerates were genetically inferior to the native population. Specifically, he proposed that the presence of immigrant germ plasm in the general population introduced risk for a wide range of criminal and delinquent behaviors such as crimes of larceny, kidnapping, assault, murder, rape, and sexual immorality (Davenport, 1911). Confident in his observations, Davenport set about rearticulating this genetic risk for society in economic terms. In 1910, he founded the Eugenics Record Office, a team of field workers who set about recording the family histories (ie, immigrant status) of asylum, prison, and poorhouse residents. Davenport had recognized that many of societies "abnormals" and "defectives" would likely have already been identified and incarcerated and as such would be easily accessible for data collection. However, he also sent his team to survey members of the general population in an attempt to discover the level of societal risk attributable to those not yet incarcerated (risk of abnormality, it seemed, resided in the community also, among the healthy, among those considered normal). Davenport estimated that the annual cost of supporting these cacogenics (poorly born) was over $100 million (taxpayer dollars). Abnormality now it seemed had a cost and importantly this was to be borne, not by those who were affected, but by those unaffected (ie, those who were normal).

The data underpinning Davenport's assertions was in part provided by his Eugenics Record Office survey team. However, Aaron Rosanoff, a doctor at King's Park State Hospital in New York provided one of the first *empirical* tests confirming Davenport's assertions regarding the heritability of deviancy, degeneracy, and insanity. Rosanoff traced the family histories of 72 insane patients. His hypothesis was that, according to Mendelian principles of genetic transmission, 33% of the tested relatives of these patients should have a documented history of mental illness. Initial testing, however, indicated that only 4% of family members met the criteria for mental illness, therefore failing to support the hypothesis. However, Rosanoff found that if the existing classification of insanity/mental illness was relaxed somewhat for these relatives then the 33% heritability prediction could be supported. In subsequent analyses, Rosanoff expanded manic-depressive illness to include more general family behaviors (ie, not specific to the assumed illness) such as being highly strung, excitable, dictatorial, abnormally selfish, awfully tempered, or blue and expanded schizophrenia to include relatives who were cranky, stubborn, nervous, queer, suspicious of friends and family, and who worried over nothing. This broader spectrum of abnormality that now encroached on normality and migrated beyond the walls of the asylums and poorhouses was termed "neuropathy." Now, armed with this new taxonomy, Rosanoff concluded that "the hereditary transmission of the neuropathic constitution as a recessive trait, in accordance with the Mendelian theory, may be regarded as definitely established" (Rosanoff and Orr, 1911).

These earliest proponents of Darwinian Theory, it seems, confidently assumed responsibility for demarcating the boundaries of normality and abnormality and for imposing this dichotomy on the public at large. They confidently declared that their propositions were empirically evidenced and grounded in theory and that theirs was a morally and scientifically justified interpretation of *social* variation. They were among the first to speculate about the biological basis and the heritability of abnormality. They were among the first to advocate action to identify and *contain* abnormality and to preserve normality. Importantly, they were among the first also (but certainly not the last) to broaden and relax their boundaries of abnormality, encroaching on normality (whatever this was), to satisfy their *scientific* assumptions.

Our attempts to understand our evolutionary past, it seems, quickly influenced action to secure our "fittest" possible future, and while this confused, elitist, and misguided interpretation of evolutionary theory for

humanity set the scene for fearing abnormality, another field had already begun to package abnormality and to speculate about its *likely* underlying pathophysiology.

Psychiatry's Normality

> *Every normal person, in fact, is only normal on the average. His ego approximates to that of the psychotic in some part or other and to a greater or lesser extent.*
>
> Sigmund Freud

While eugenicists' impulsive and erroneous translations of Darwinian theory guaranteed long term confusion over the existence and boundaries of ab/normality, psychiatry further compounded societal misunderstanding through their repeated attempts to identify and contain abnormality. A turbulent history of endorsing and promoting competing philosophies on the form and origins of abnormality ensured that normality and abnormality soon became deeply confused and often indistinguishable constructs. More importantly, psychiatry's ultimate decision to adopt a disease-based model of psychopathology and their obstinate axiomatic stance on the biological basis of abnormal psychological functioning ensured that both normality and abnormality would not only remain a mystery to society, but would remain beyond psychiatry's reach also.

Long before Galton's proclamations regarding the preservation of the fittest in society, psychiatry had begun to speculate about the physiological basis of the mind (the *abnormal* mind). In 1812, Benjamin Rush, considered to be the founding father of psychiatry, authored *Medical Inquiries and Observations upon the Diseases of the Mind*. Psychiatry, to begin, adopted a biomedical model of human psychology and confidently referred to *diseases of the mind* when evaluating the unusual, anomalous, and abnormal behaviors of those in their care. Rush speculatively proposed that insanity was located in the blood and that manipulation of blood flow would alleviate the observable distressing psychological states of, for example, mania and delusion (too much blood) and indolence and apathy (too little blood). However, while psychiatrists from the outset conjectured about the potential physiological basis of that which they investigated, they were entirely and frustratingly reliant upon observation of overt human behavior alone. In 1844, the Association of Medical Superintendents of American Institutions for the Insane (which would later become the American-Medico Psychological Association and then ultimately the American Psychiatric Association) declared that insanity was something that was easily recognized and distinguishable from normal functioning but not easily classified (Grob, 1991).

A major problem for psychiatry early on was that their asylums housed a diverse array of individuals who exhibited and were characterized by a diverse array of unusual experiences. While insanity was commonly referred to and documented in the medical literature, those labelled insane were often very different from one another. Moreover, psychiatrists also encountered and were charged with treating cases of syphilis, alcoholism, senility, and mental/intellectual disability. Abnormality, as it existed in these asylums, it seemed, was a complex, convoluted mix of behaviors that did not lend itself easily to coherent classification.

One of the earliest taxonomies of insanity was proposed in 1885 whereupon eight separate categories were identified. In an attempt to impose some order on the wide range of unusual experiences expressed by those inhabiting the asylums of the day, psychiatrists attempted to diagnostically group behaviors into those that characterized mania, melancholia, monomania (a form of partial insanity conceived as single pathological preoccupation in an otherwise sound mind), dementia, general paralysis of the insane (caused by late stage syphilis), epilepsy, toxic insanity, and congenital mental deficiency (intellectual disability). While most of these disease categories could be evidenced over time to be physiological in nature, those that could not offered little by way of physical evidence to support traditional disease-based hypotheses. Psychological abnormality was identifiable and recognizable at a behavioral level only, and until empirical evidence suggested otherwise, these particular categories of abnormality would remain elusive. Early on, it seems, those in pursuit of a classification system of abnormal psychological functioning acknowledged that they were "forced to fall back upon the symptoms of the disease—the apparent mental condition, as judged from the outward manifestations" (Grob, 1991). Recognizing the severe limitations of a medical discipline responsible for medically treating abnormality, but with restricted ability to medically identify and classify it, psychiatry had to find a way to reliably navigate the construct.

While a language of disease seemed momentarily to predominate, psychiatry, bereft of the necessary anatomical and biochemical evidence needed to sustain their early disease-based assumptions, deviated and stressed instead the importance of the environment and our subconscious capacity for defense. Sigmund Freud's psychoanalysis arrived, dominated psychiatric practice and began to influence many of psychiatry's new formulations of abnormal psychological functioning. Psychiatry now began to prioritize the psychology, rather than the physiology of abnormal and atypical behavior. With the introduction of psychoanalysis, psychiatry's more traditional, physiologically based divisions between normality and abnormality had suddenly become a little less clear.

However, while Freud's teachings dominated, others in psychiatry were more resistant and ardently worked to reestablish a disease-based model of psychopathology. In 1883, a German psychiatrist, Emil Kraeplin, attempted to classify some of the most perplexing behaviors and experiences encountered by psychiatrists. Authoring *A Compendium of Psychiatry* (later to become *A textbook of psychiatry for physicians and students*), Kraeplin dismissed Freud's psychoanalytic approach to psychological distress and abnormal functioning as subjective and unscientific and instead advocated the long-term observation of patients and their expressed symptomologies.

Kraeplin proposed that symptoms which emerged together and changed uniformly with one another over time offered the most plausible basis upon which to identify discrete disease entities and importantly to explore their underlying etiologies and likely disease courses. He distinguished between two separate and distinct symptom profiles, manic-depression and dementia praecox. Kraeplin observed that patients whose symptomologies were largely characterized by affect (fluctuations in mood from deep depression to manic elation) seemed to recover over time and that their prognosis was often reasonably benign. Others, however, seemed to exhibit a distinct lack or loss of affect and experienced impaired motor functioning. These individuals also, however, would experience a much more malign outcome and eventually become chronically ill and senile (dementia praecox = senility of the young). Kraeplin was the first to attempt to achieve both reliability (the accurate identification and classification of psychological disease) and validity (the accurate prediction of disease course and outcome) in the pursuit of meaningful diagnosis. Importantly, he also proposed that while his original classification system was symptom based only, the underlying physiological/neurological basis of these diseases would ultimately be identified in time (now that psychiatry knew where to look).

Psychiatry now proposed two competing causal philosophies on the origins of psychological abnormality. From a Freudian perspective, psychological abnormality was assumed to be consequential to internal conflict that arose from understandable reactions to one's past and environment, whereas Kraeplinian teachings proposed that psychological abnormality was physiologically distinguishable from normal functioning and that it ultimately signaled disease. Regardless, proponents of both positions struggled to adequately make sense of the multiple constellations of supposed *symptoms* that those in their care were manifesting.

In an attempt to contain and describe abnormal functioning more coherently and comprehensively, psychiatry introduced the Statistical Manual for the Use of Institutions for the Insane in 1918. This manual identified 22 separate groups of psychiatric disorders. Notably, the manual distinguished between disorders that were biological in nature (20 groups of disorder) and those that were without an identifiable underlying biology (2 groups of disorder). These latter two groups of disorder were intended primarily to discriminate between psychologically distressed patients who exhibited psychosis and those whose symptom presentations were devoid of psychosis. Importantly, however, this earliest of classifications proposed that certain psychologically abnormal states and behaviors were distinguishable from others on the basis of a recognizable and measureable underlying pathophysiology. That which was manifested psychologically therefore often had a detectable physiological cause, but often much that was manifested psychologically revealed no obvious biology. Biology, it seems, had been and would continue to be the basis upon which the battle lines for psychological abnormality would be drawn.

Until this time, psychological abnormality mostly resided and was treated in the asylums of the day. However, given the popularity of Freud's teachings, it was soon to become evident that people in the community could also benefit from psychiatric care. In 1946, psychiatry moved beyond the walls of the asylums and hospitals and began treating the psychologically distressed in the community. William Menninger, for example, noting the transient and temporary nature of the often extreme psychological distress experienced by many who returned home from the Second World War, in 1946 established the Group for the Advancement of Psychiatry. Menninger, a US military psychiatrist, proposed that many in the general population would benefit from psychiatric assistance to help them to deal with the many daily stresses and traumas of life. Championing the psychological treatment of the general public, Menninger helped moved psychiatry into the community, and with this, psychiatry now publically acknowledged that psychological abnormality was in fact often quite common, and often recoverable. The distinction between psychological normality and abnormality had now become even more ambiguous. Those in receipt of psychiatric care in the community were now recognized to be *psychologically distressed*; they were not, it seemed, to be considered *abnormal* (insane) in the traditional asylum sense of the word.

Psychiatry introduced the first edition of its *Diagnostic and Statistical Manual* (DSM-I) in 1950. Notably, this first manual, similar to the Statistical Manual for the Use of Institutions for the Insane published in 1918 and consistent with the psychoanalytic climate of the time, distinguished between mental disturbances that were organic in nature (eg, abnormal psychological behavior as a consequence of infections, poisoning, intoxication, circulatory and metabolic problems, brain cancers, multiple sclerosis, etc.) and those that seemed to be related to an individual's adjustment to their environment. In an attempt to order and make

sense of this nonorganic abnormality, the DSM subdivided patient experiences into psychotic (manic-depressive; paranoid; and schizophrenic reactions) and psycho-neurotic disorders (anxiety; obsessions and compulsions; depression; emotional instability). Importantly, once again, anxiety, depression, and psychosis according to this manual were not attributable to an underlying physiological disease but instead reflected emotional distress attributable to internal conflicts, adjustments to environmental stressors, and traumatic/stressful life histories. Psychotic and psychoneurotic disorders, while visibly distinct from normal psychological functioning, were now, however, also firmly recognized as distinct from the many organic-based psychopathologies.

It seems therefore that early on much of psychiatry could not discriminate between normal and abnormal psychological functioning at a physical level and so instead viewed abnormal psychological functioning as behavior that was consequential to life adjustment and understandable reactivity to the environment. This, unsurprisingly, largely complicated the distinction between normality and abnormality. As Whitaker and Cosgrove put it "there was no longer a clear line that divided the mentally well from the mentally ill, and if anything, it seemed that unresolved psychological conflicts probably plagued most people, at least to some degree [and at some time]" (2015; p. 13).

Still advocating Freudian principles, psychiatry continued to attempt to contain and package abnormality, reconfiguring and refining diagnoses in an attempt to accurately describe the many forms of mental disturbance they encountered. Psychotic disorders were repeatedly revised: from Kraeplin's dementia praecox, to Bleuler's schizophrenia, to Schneider's first rank symptoms of hallucinations and delusions. Klaus Leonhard's bipolar disorder replaced manic-depressive disorder, and the psycho-neurotic disorders soon evolved into the anxiety disorders (phobias, generalized anxiety disorder, and obsessive compulsive disorder) and nonpsychotic depression. Psychiatry had constructed many identities for these nonorganic disorders of abnormal psychological functioning; however, their inability to reliably classify these constructs was about to come under heavy fire.

Continued revisions of the DSM (DSM-II was introduced in 1968), based predominantly on clinical observation, soon began to falter as researchers began to challenge the reliability and utility of the new diagnoses. Many researchers specifically challenged the symptom composition and discriminatory power of the diagnoses and questions also began to arise regarding diagnostic consensus among psychiatrists and consistency in diagnosis from country to country. In 1962, Aaron Beck, for example, reviewed a series of studies that had evaluated the reliability of psychiatry's nonorganic disorders contained within the DSM and found that diagnostic agreement among psychiatrists ranged from only 32–42%. In 1968, Donald Bannister drew attention to the growing confusion and misunderstanding surrounding DSM classification stating that "We diagnose one person as schizophrenic because he manifests characteristics A and B and diagnose a second person as schizophrenic because he manifests characteristics C, D, and E. The two people are now firmly grouped in the same category while not specifically possessing any common characteristic….Disjunctive categories are logically too primitive for scientific use" (Bannister, 1968).

Notably, researchers had also begun to reveal grave discrepancies in diagnoses between psychiatrists from different countries. For example, Copeland et al. (1971) revealed that when 134 US and 194 British psychiatrists were given a description of a patient, 69% of the US psychiatrists diagnosed "schizophrenia," but only 2% of the British Psychiatrists did so. Cooper (1972), moreover, documented that psychiatrists in Great Britain and the United States were twice as likely as psychiatrists in Russia to diagnose the disorder. Diagnosis was not working, and clinicians were not arriving at the same conclusions when evaluating their patients. Diagnostic reliability and consensus among those administering the diagnoses was proving problematic. Nonorganic psychological abnormality it seems, was not easily contained after all, and if discriminating between their different constructions of abnormality was proving problematic, psychiatry (and society) was soon to confront something much more challenging.

Rosenhan's Normality

> *We now know that we cannot distinguish insanity from sanity.*
>
> David Rosenhan

In 1973, psychiatry confronted and diagnosed *normality*. In a landmark study entitled "On being sane in insane places," David Rosenhan, a Stanford University psychologist, along with eight associates (a psychology graduate student, three psychologists, a pediatrician, a psychiatrist, a painter, and a housewife), none of whom had a history of mental illness, attempted to gain admission to 12 different psychiatric hospitals across the United States. The 12 hospitals were located in five different states on the East and West coasts of the United States. Some were old and shabby, some were quite new, some had good staff-patient ratios, and others were quite understaffed. One was a reputable private hospital. Each "pseudopatient" claimed that they heard voices that seemed to say the words "empty," "hollow," and "thud." No other psychiatric symptoms were reported.

All eight pseudopatients successfully gained admission to their respective hospitals, and all but one were diagnosed with schizophrenia (one was diagnosed with manic-depressive psychosis). Each was instructed to "act normally" once admitted and to report that they felt fine and no longer heard voices. Despite constantly and openly taking extensive notes on the behavior of the staff and other patients, none of the pseudopatients were identified as impostors by the hospital staff, although many of the other psychiatric patients seemed to be able to correctly identify them as impostors. In the first three hospitalizations, 30% of the patients expressed a suspicion that the pseudopatients were sane, with some suggesting that the patients were researchers or journalists investigating the hospitals. Hospital notes obtained after the experiment indicated that all pseudopatients were characterized as friendly and cooperative by staff. However, records also indicated that staff interpreted much of the pseudopatients' behavior in terms of their diagnoses. For example, one nurse labelled the note-taking of one pseudopatient as "writing behavior" and considered it pathological (Rosenhan, 1973).

Their stays ranged from 7 to 52 days, and the average stay was 19 days. All were discharged with a diagnosis of schizophrenia "in remission." Rosenhan noted that "The label 'in remission' should in no way be dismissed as a formality, for at no time during any hospitalization had any question been raised about any pseudopatient's simulation. Nor are there any indications in the hospital records that the pseudopatient's status was suspect. Rather, the evidence is strong that, once labelled schizophrenic, the pseudopatient was stuck with that label. If the pseudopatient was to be discharged, he must naturally be 'in remission'; but he was not sane, nor, in the institution's view, had he ever been sane" (1973; p. 257).

In a follow-up study, Rosenhan approached a well-known research and teaching hospital, whose staff had heard of the results of the initial study but claimed that similar errors could not be made at their institution. Rosenhan therefore invited the hospital to participate in a new study. Hospital staff were informed that one or more pseudopatients would attempt to gain admission to their hospital within a 3-month period. The staff were asked to rate every incoming patient and to assess the "legitimacy" of their symptom presentations. After the 3-month period the hospital reported that 21% of those assessed (193 in total) were pseudopatients, while a further 22% were considered suspect. In reality, however, Rosenhan had sent no pseudopatients, and all patients suspected as impostors were ordinary patients. This led to a conclusion that "any diagnostic process that lends itself too readily to massive errors of this sort cannot be a very reliable one."

Rosenhan concluded, "It is clear that we cannot distinguish the sane from the insane in psychiatric hospitals," and he suggested that the use of community mental health facilities that concentrated on specific problems and behaviors rather than psychiatric labels might be a more meaningful way forward for psychiatry. While for decades psychiatry had been struggling to demarcate the boundaries between multiple constructs of abnormality, Rosenhan's studies suddenly and dramatically revealed to society that the boundaries between normality and abnormality were every bit as challenging to establish, if not more so.

Rosenhan, however, was not alone in challenging the status quo. Challenges also came from psychiatrists like Thomas Szasz (1960), who argued that mental illness was a myth, used to disguise moral conflicts. Sociologists such as Erving Goffman (1968) argued that mental illness was merely another example of how society labels and controls nonconformists. Moreover, behavioral psychologists challenged psychiatry's fundamental reliance on unobservable phenomena, and gay rights activists criticized the APA's listing of homosexuality as a mental disorder.

DSM's Normality

> *Despite extensive field testing of the DSM-III diagnostic criteria before their official adoption, experience with them since their publication had revealed, as expected, many instances in which the criteria were not entirely clear, were inconsistent across categories, or were even contradictory.*
>
> APA (1987: xvii)

In the aftermath of Rosenhan's revelations and as a response to the growing evidence base challenging the reliability of psychiatric diagnoses, those responsible for the DSM sought to revise their classification systems once more. Initially the impetus was to make the DSM nomenclature consistent with the International Statistical Classification of Diseases and Related Health Problems, published by the World Health Organization (ICD is used more widely in Europe and other parts of the world and first documented mental disorder in its sixth revision in 1949 around the time of DSM-I). On this occasion, psychiatry and the APA would attempt to minimize disagreement between clinicians, both domestically in the United States and internationally, by imposing strict symptom checklist criteria. Hoping to remove clinician subjectivity and speculation about symptom presentation and diagnosis, the third revision of the DSM (DSM-III introduced in 1980) instructed clinicians explicitly on symptom classification. Clinicians now received clear guidance regarding the appropriate diagnostic allocation of symptoms. Moreover, in addition to these symptom checklists, clinicians were also explicitly instructed on how to question their patients. Structured clinical interview schedules were introduced to ensure that clinicians conformed and adhered to a common,

shared formulation process. Diagnosis, now it seemed, would become consistent, diagnosis now finally would become reliable.

The Diagnostic and Statistical Manual continued to be revised and updated, and in the years following DSM-III, four subsequent editions emerged. DSM-III-R (Revised DSM-III, 1987), DSM-IV (1994), DSM-IV-TR (Text Revision, 2000) and DSM-5 (2013) would each successively repackage psychological abnormality to ensure that signs and signals of atypical psychological functioning (symptoms) were carefully grouped and classified to discriminate one assumed disorder from another. However, while increased reliability continued to satisfy the *administrative* objectives of classification, diagnostic validity failed to be established. As a consequence today and entirely because of this validity crisis, we know of no diagnosis-specific causative agents and no disease-specific cures for common types of mental disorders.

The diagnostic manuals are replete with serious limitations. The most recent classifications (DSM-5 and ICD-11), for instance, list several hundreds of diagnostic categories; however, evidence shows that most of these are rarely used (Moller et al., 2007; Munk-Jorgensen et al., 2010). Moreover, despite the wide variety and selection of diagnoses available, many who seek and need clinical assistance fail to qualify for a specific diagnosis, while many others often require more than one diagnosis to adequately describe their problems. Psychiatry's attempts to contain abnormality since DSM-III therefore introduced a wide array of new classification problems that continued to keep the construct(s) of ab/normality out of reach.

This continued confusion with diagnostic classification has been evidenced most clearly by findings from large-scale epidemiological studies. These studies have been designed to evaluate the presence and variation of psychiatric symptoms and diagnoses in the general population and have been conducted worldwide. The findings from these studies have revealed that mental disorders, as defined in DSM and ICD classification manuals, are surprisingly common and that most individuals who qualify for a diagnosis actually qualify for multiple diagnoses. According to these studies, abnormality seems to be widespread, and those who are *afflicted* are likely to suffer from a range of supposedly discrete disorders. For example, recent analytic findings based on the National Comorbidity Survey—Replication (NCS-R; a nationally representative community household survey of over 9000 US citizens) revealed that 57% of those surveyed had a lifetime diagnosis of at least one mental disorder. Moreover, those with a diagnosis were likely on average to have three separate diagnoses (Harvard School of Medicine, 2005). Such findings are consistent with those from other epidemiological surveys conducted in Australia (eg, Andrews et al., 2001), New Zealand (eg, Newman et al., 1996), and across Europe (eg, Germany, Jacobi et al., 2004).

However, surprisingly, such cross-sectional findings are believed to be underestimates. Other researchers have demonstrated that if individuals are analyzed prospectively, that is over time, then it is likely that the *majority* of people in the general population will actually be evidenced to suffer from a diagnosable mental disorder at some point in their lives (Copeland et al., 2011; Moffitt et al., 2011). Incidentally, many more individuals in these studies have been evidenced to experience a wide array of supposed symptoms but do not meet the strict diagnostic "cut-off" criteria required for diagnosis. Such variation has led many researchers to suggest that many supposed disorders may actually reflect extremes of continuously distributed phenomena throughout the population. From this perspective, even the most severe psychological experiences can be evidenced to exist at low, moderate, and clinical levels (Murphy et al., 2009, 2012). While psychiatric nosologies therefore such as the DSM and ICD are predicated on the view that mental disorders are categorically distinct, these epidemiological findings indicate that it is often far more common to find multiple rather than single discrete diagnoses (Hasin and Kilcoyne, 2012; Kreuger and Markon, 2011). According to Uher and Rutter (2012), "this 'everything predicts everything' result suggests that it is unlikely that the various disorders represent separate entities or that major causative factors could be specific to [any] particular diagnosis" (p. 592).

Researchers recently have begun to focus more attention on assessing whether this high degree of observed co-occurrence (comorbidity) between supposed disorders and symptoms can be explained by more broad, overarching constructs (called factors or dimensions). This approach is similar to the popular psychological personality trait theories whereby a number of superordinate latent personality dimensions (eg, openness, conscientiousness, agreeableness, extraversion, neuroticism, and psychoticism) were hypothesized to explain the high degree of association between specific observable personality traits/characteristics (Costa and McCrae, 1992; Eysenck and Eysenck, 1976). Krueger et al. (1998), for example, hypothesized that adult psychological problems could be explained in terms of two superordinate psychopathology factors: internalizing and externalizing. The internalizing factor/dimension is proposed to comprise problems of negative emotion and includes distressing psychological experiences such as depression, generalized anxiety, phobias, posttraumatic stress, and panic. The externalizing factor/dimension, on the other hand, is proposed to comprise difficulties in behavioral inhibition and includes distressing psychological experiences such as substance dependence and abuse, conduct problems, and antisocial behavior. Since the initial study by Krueger et al. (1998),

multiple studies within different adult populations have revealed this two-factor model of psychological distress (eg, Forbush and Watson, 2013; Kendler et al., 2003; Kreuger and Markon, 2011).

However, researchers have also suggested the presence of a third superordinate factor, psychosis. The suggestion of a psychosis dimension is based on a large body of evidence indicating that psychotic experiences exist along a continuum in the general population (van Os et al., 2009) and are commonly observed alongside other nonpsychotic experiences (Murphy et al., 2012). This dimension is characterized by perceptual anomalies and delusional beliefs and includes assumed disorders such as schizophrenia, bipolar disorder, thought disorders, and obsessive compulsive disorder. For example, in a study of 469 participants from the Suffolk Mental Health Project, Kotov et al. (2010) found evidence to support three underlying factors, labelling them internalizing, externalizing, and schizophrenia. In a follow-up study, utilizing a larger sample ($N = 2900$) from the Improved Diagnostic Assessment and Service project, Kotov et al. (2011) replicated their findings, once again identifying the three dimensions. More recently, Fleming et al. (2014) analyzed the National Comorbidity Survey data ($N = 5877$) from the United States, using both exploratory factor analysis and confirmatory factor analysis, and again found support for three correlated factors of internalizing, externalizing, and psychosis.

While a large body of evidence now supports a dimensional representation of psychopathology, consensus regarding the precise number of dimensions and their hierarchical structure has yet to be reached. To date, wide-scale variation in dimensional representations of psychopathology has been evidenced. This variation often has been attributable to factors such as (1) the number and type of disorders being modelled, (2) the samples from which the data has been derived (eg, whether they have been clinical or nonclinical samples), (3) the rating instruments used, (4) the phase of *illness* experienced by the samples, and/or (5) the statistical procedures applied to the data. Moreover, while various discrete dimensions have been evidenced to adequately account for the co-occurrence of abnormal psychological phenomena, recent bi-factor models seem to suggest the presence of a more dominant underlying general dimension (eg, Caspi et al., 2014). This general dimension seems to account for the co-occurrence of disorders that regularly occur across discrete dimensions. It seems therefore that while latent dimensional models have advanced representations of psychological abnormality from discrete overlapping diagnoses to more general dimensions of co-occurrence on the one hand, they have on the other also created an equally perplexing common factor to contend with. Somewhat unexpectedly therefore, while dimensionality has clarified much of our confusion regarding the erroneous and spurious diagnosis of atypical psychological functioning, it has also reminded us of the often extreme variation and flexibility of human experience.

Attempting to apply biomedical principles to the classification and treatment of psychological and emotional distress, psychiatry it seems, relentlessly pursued a disease-based model of psychological functioning without the requisite physiological and biochemical evidence that other branches of medicine so fundamentally relied upon. In doing so, psychiatry assumed an axiomatic stance on the biological origins of psychological abnormality and committed itself to a fixed and inflexible framework of investigation. Atypical psychological functionning according to the profession reflected disease, biological breakdown, and malfunction, and if the available evidence of the day did not support this assumption, the underlying biology, it was maintained, would reveal itself in time. The absence of this evidence and the wide-scale prevalence of *abnormality* in the general population has seriously undermined this classification system but has also raised important questions regarding the assumed boundaries between sanity and insanity and between normality and abnormality.

PART TWO

According to this brief history, normality's flexibility as a psychological construct seemed to be attributable to a number of factors. First, we crudely dissected humanity and society based on impulsive and erroneous translations of Darwinian theory. Second, we seemed to assimilate much of what we believed to be socially atypical into our conceptions of abnormality. Criminality, severe intellectual disability, homosexuality, poverty, and psychological and emotional distress all seemed to be acceptable candidates. Third, from our earliest attempts to measure human psychology following Darwin's revelations about the origin of species, it seems we sidestepped normality and instead persisted in and prioritized the scientific investigation of psychological disease and compromised inheritance. Moreover, we did this in spite of a continued lack of evidence to support such a direction. Fourth, normality's flexibility often seemed attributable to our frequent deviation from and neglect of the scientific method when investigating behaviors *deemed by society* to be atypical. Accepted scientific principles of systematic observation and measurement and the formulation, testing, and modification of hypotheses were repeatedly relaxed and often violated in our pursuit of ab/normality. Fifth, from the very beginning, we seemed to achieve an unspoken, undocumented consensus regarding what abnormality was, and more importantly regarding who exhibited it. Abnormality, however, was then, and still remains, socially determined.

We never achieved a sound, evidence-based and scientifically validated conceptualization of the construct. Instead, when it came to our contemplation of ab/normality, we seemed simply to remain satisfied with "a sense of familiar recognition and false familiarity" (Frances, 2013).

This last reason is a particularly pertinent one. As a species, we seem to simply "know" abnormality when we encounter it, and we are quite happy to entertain proposals of defective inheritance and broken neurology to account for it. This false familiarity and resigned investment in perceived ab/normality suggests that our perception and detection of ab/normality may be a fundamental part of who we are.

Ethnocentrism's Normality

> *But then with me, the horrid doubt always arises whether the convictions of man's mind, which has been developed from the mind of the lower animals, are of any value or at all trustworthy.*
>
> Charles Darwin

Man's mind, while certainly evolved from the lower animals, is still subservient to many of the same evolutionary forces that maintain and enhance "fitness" for all animals. Investment in mate choice, kin support, and social rank, etc., much like other species, underpin much of what we do and who we are as a species. However, our articulation of human form and function has too rarely acknowledged these ubiquitous and most primitive goals. Instead, we have elected to articulate human form and function based on only recently acquired cognition, that is, our perception and interpretation of overt, observable traits, beliefs, and behaviors. We have elected to package and classify human form and function based on our evaluative perceptions of what is familiar or different, common or uncommon, expected or unexpected. For too long, we have neglected to realize that all that we perceive, experience, and attempt to classify is dictated ultimately by these latent primitive drives.

Normality and abnormality seem intuitively recognizable and understandable. Furthermore both constructs seem woven into our daily perceptions, judgements, and decisions. In psychology, for example, everyday expositions of normal make reference to that which is perceived to be conventional, standard, ordinary, and regular. Importantly, such expositions also make reference to that which is common, familiar, and expected. Moreover, we seem to have an innate preference for normal. However, as we have seen, psychological expositions of normality have also often been articulated through a language of abnormality. That which is perceived to be aberrant, anomalous, atypical, and bizarre is also likely to be that which is both uncommon and unexpected, and we seem certainly to have an aversion to this. Interestingly, this explicit language of evaluative perception, couched in a context of expectation and familiarity, reveals much about the concept of ab/normality itself.

From an ethnocentric perspective, our current formulations and articulations of ab/normality resonate with much of what evolutionary theorists have revealed to us about human nature. That which enhances our fitness as a species largely dictates what we perceive and experience, and these perceptions and experiences, in turn, largely dictate our value judgements and decisions (ie, what we perceive and experience to be normal or abnormal). Donald Hoffman's (2012) fascinating visual perception experiments provide a wonderful demonstration of the import of fitness in our perceptions of the world and our creation of reality. Hoffman has eloquently shown that we as a species, rather than perceiving reality, actually instead perceive fitness. Perceived fitness therefore offers an alternative vantage point from which to view these social conceptions of normality and abnormality. However, rather than arbitrarily segregating one concept from the other, this approach distinguishes instead between the primitive underlying adaptive context of human behavior and the advanced and sophisticated neurological *hardware* that permits humans to attempt to make sense of this behavior. From this perspective, perceived normality and abnormality are essentially manufactured cognitions that aid us in our social navigation of our space and of one another. However, this neurological representation of the world often also disguises and hides the rudiments of our basic drives, to survive and reproduce.

Normality's Bias

> *Evolution cares little about logic.*
>
> Paul Gilbert

Neurological sophistication is that which truly distinguishes our species from others. Specifically, the evolution of the prefrontal cortex and its affordances for logic and reasoning, which has permitted humans to differentiate between conflicting thoughts, to determine the difference between what is "good" and "bad," better and best, same and different, seems to have dramatically enhanced human fitness and has enhanced proficiency in pursuing a range of biosocial goals (such as mating, establishing social status, and caring for offspring). The environment, it seems, for humans, has favored logic. However, importantly, when it comes to the human capacity for contemplation, for conceptualizing, and entertaining the existence of ambiguous and confusing constructs such as normality, or questioning the very nature of our own existence, evolution cares little about logic. What evolution does favor is bias.

What we perceive and experience, how we perceive and experience it, and why we perceive and experience what we do is dictated by multiple, primitive, self-serving and group biases. Gilbert (1998) notes that biases are an integral part of our information processing systems that tune attention to certain cues, calculate risks and benefits to certain signals, and select strategies. Importantly, Gilbert also reminds us that these biases are not rooted in logic. While we may experience preferential and aversive thoughts and emotions in relation to our environment and those that inhabit it, we need not necessarily have direct conscious access to the source of these preferences and aversions. Our observations of others' behaviors therefore and our subsequent evaluations are often dichotomized on the basis of familiarity and unfamiliarity.

For example, in-group/out-group biases (the tendency to distinguish self and others on the basis of group membership) have long been evidenced to show that once individuals have identified with a particular group they tend to invest solely in that group and see it as superior to others (van der Dennen, 1987). Evidence indicates that groups may seek to dominate other groups, defend their own interests, and attempt to limit subordinate groups' access to resources (Pratto et al., 1994). In the context of aberrant, anomalous, atypical, and bizarre behavior, we as a species have likely imposed our own in/out status and have acted/reacted accordingly (ie, engaged or avoided). This ethnocentric profile of human interaction has often been observed and evidenced in the context of societal reaction to and (in)tolerance of abnormal psychological behavior (ie, mental *illness*) (Watson et al., 2003; Ottati et al., 2005). Interestingly, some authors argue that the importance of markers that are both easily visible and difficult to imitate may mean that physical/biological characteristics are preferred to cultural traits as a basis for group differentiation (see van den Berghe, 1996; cited in Axelrod and Hammond, 2003).

Therefore, it is possible that our early investment in a disease-based model of abnormal psychology has facilitated group differentiation between the psychologically well and the unwell simply by suggesting that unusual psychological traits and characteristics are neuropathological in nature. Notably, Read et al. found that individuals in the general population who believed in a biological basis of mental disorder held more stigmatizing views toward those who possessed a psychiatric diagnosis. Contrary to the assumptions on which most de-stigmatization programs have been based, Reads findings demonstrated that biological and genetic causal beliefs in the population were related to negative attitudes, including perceptions that "mental patients" were dangerous, antisocial, and unpredictable (Read and Harré, 2001; Read et al., 2006). Multiple other biases (eg, biases in care provision and care seeking, biases in intersexual and intrasexual attraction, competitive biases, and reciprocal exchange biases) have also been evidenced to underpin our perceptions, experiences, and evaluations of what is normal and what is not.

From this perspective, it seems most likely that, as humans, we were always destined to construct and perceive ab/normality. Many evolutionary theorists have contributed greatly to this field and have offered insightful and valuable reminders of the role of these biases in evolved and evolving behavior and cognition. This work offers a rich account of the landscape of perceived ab/normality, and the many biases evidenced to underlie human behavior and cognition provide a useful lens through which to inspect the construct. While innate ethnocentrism therefore may have accounted for our receptiveness to and our investment in such an ambiguous and illusive construct as ab/normality, one factor seems to be responsible for sustaining confusion in the construct more than any other, and that is our erroneous belief that the adaptive goal of normal functioning is to be happy and to be without suffering and distress (Gilbert, 1998; Bateson et al., 2011).

Suffering, distress, and reduced quality of life need not always indicate pathology or malfunction, and this fact more than any challenges the very foundations of what we have believed psychological normality and abnormality to mean. An absence of detectable chemical or anatomical dysfunction certainly suggests that human psychology that appears abnormal and atypical must therefore be different from the norm or the typical for some other reason. Evolutionary psychology offered one possible explanation, and it centered on our adaptive nature and our ability to respond to our complex social environments.

Evolution's Normality

> *We must, however, acknowledge, as it seems to me, that man with all his noble qualities… still bears in his bodily frame the indelible stamp of his lowly origin.*
>
> Charles Darwin

Evolutionary explanations and theories have been proposed for many alleged "pathologies" of the mind including mood disorders (see Nettle and Bateson, 2012), psychosis (see Kelleher et al., 2010), social anxiety (see Gilbert, 2001) and phobias and anxiety (see Bateson et al., 2011). What many of these theories offer is an alternative explanation of what we perceive abnormality to be. Rather than viewing atypical psychological functioning and behavior as a signal of probable brain pathology, evolutionary models instead consider the evolved, adaptive responsivity of behavior to challenging and ever changing environmental demands. Abnormality from this perspective, importantly, becomes anchored to and silhouetted by an evolutionary context, and

as a consequence, many behaviors that might once have seemed unusual, strange, or aberrant instead appear resilient and adaptive and, given the context, impressively normal.

A substantial and growing literature now informs our understanding of the potential adaptive nature of many behaviors and cognitions long believed to reflect disease, nonadaptive error, or malfunction. While for decades disorders such as depression, anxiety, and psychosis have each remained the focus of distinct and often separate lines of investigation (from, eg, neurobiological, genetic, and psychosocial research perspectives), each has also been carefully considered from an evolutionary perspective. The emerging evidence from these evolutionary lines of investigation suggests that normality's flexibility actually often more accurately reflects our adaptability and that what we often perceive to be abnormal is actually behavior that reflects, for example, energy/resource conservation, social competition, attachment, avoidance of social risk and exclusion, social defense, submission, vigilance and hypervigilance, isolation, and creativity.

The Normality of Resource Conservation

A number of esteemed authors have eloquently described depression and anxiety from the perspective of energy and resource conservation. Seligman (1975), for instance, proposed an animal model of how learned helplessness may manifest itself as depression and anxiety. According to Seligman, "Learned helplessness is a behavior in which an organism forced to endure aversive, painful or otherwise unpleasant stimuli, becomes unable or unwilling to avoid subsequent encounters with those stimuli, even if they are escapable. Presumably, the organism has learned that it cannot control the situation and therefore does not take action to avoid the negative stimulus. Learned helplessness theory [therefore] is the view that clinical depression and related mental illnesses may result from a perceived absence of control over the outcome of a situation. Organisms [therefore] that have been ineffective and less sensitive in determining the consequences of their behavior are defined as having acquired learned helplessness" (Carlson, 2010, p. 409).

Focusing specifically on depression, Leahy (1997) proposed an investment model of depressive resistance [where] "depressed individuals believe they have few present and future resources and low utility of gain in a market that is volatile and downward sloping. Depression [from this perspective] is viewed as a strategy to avoid further loss, resulting in active attempts to resist change as evidenced in motivated negative cognition. Depressives [therefore according to Leahy] take a risk-averse strategy to minimize loss, utilizing high stop-loss criteria and rejecting optimism as a high exposure position. Unlike optimistic individuals who believe that there are many replications over a long duration to obtain gain, depressives [according to Leahy] have low diversification, high information demands, and utilize hedging, waiting, hiding and other tactics to minimize risk" (p. 3).

Also considering depression from a point of resource conservation, Nesse (2000) noted that "many functions have been suggested for low mood or depression, including communicating a need for help, signalling yielding in a hierarchy conflict, fostering disengagement from commitments to unreachable goals, and regulating patterns of investment. A more comprehensive evolutionary explanation [according to Nesse] may emerge from attempts to identify how the characteristics of low mood increase an organism's ability to cope with the adaptive challenges characteristic of unpropitious situations in which effort to pursue a major goal will likely result in danger, loss, bodily damage, or wasted effort. In such situations, pessimism and lack of motivation may give a fitness advantage by inhibiting certain actions, especially futile or dangerous challenges to dominant figures, actions in the absence of a crucial resource or a viable plan, efforts that would damage the body, and actions that would disrupt a currently unsatisfactory major life enterprise when it might recover or the alternative is likely to be even worse" (p. 14).

The Normality of Skewed Fitness

Nesse also considered the evolutionary status of psychosis and suggested that "strong recent selection for social cognition may well explain the persistence of genes that predispose to schizophrenia. [From this perspective] the specific mechanism responsible may be a skewed fitness function in which selection pushes the mean for advantageous mental traits perilously close to a "fitness cliff" where the system fails catastrophically in some individuals… strong tendencies to use metarepresentation and ToM [Theory of Mind] increase the ability to predict other people's behaviors, how they might be influenced, and how they might be trying to manipulate you. [According to Nesse] it is only one step further, over the cliff's edge of psychotic cognition, as it were, to finding secret meanings and evidence for conspiracies in other people's most casual gestures, to believing idiosyncratic grand theories and religions, and to thinking that others are controlling your thoughts" (2004; p. 862).

The Normality of Social Competition

John Price was the first to promote the idea of *social competition* to account for many of the expressed forms of abnormal psychological functioning. In a 1967 paper entitled "The dominance hierarchy and the evolution of mental illness," Price noted that "In our evolution, we passed through a stage in which small social groups were

regulated by strict dominance hierarchy… For their stability, hierarchies require certain behavior patterns from their members: irritability toward inferiors, anxiety toward superiors, elation on going up the hierarchy and depression on going down. Because of the great survival advantage to the group which a well-functioning hierarchy provides, these behavior patterns have been strongly selected for. Equilibrium was reached when the advantage they provided was balanced by the disadvantage of excess of such behavior. These excesses are manifested as mental illness; excesses of stable dominance hierarchy behavior as the chronic illnesses such as anxiety neurosis, schizophrenia, and aggressive personality; and excesses of the behavior associated with changes in the hierarchy as the phasic mental illnesses such as mania and depressive psychosis. The main prediction from [Price's] hypothesis is that factors which increase or reduce dominance hierarchy behavior will have malignant or beneficial effects on mental illness" (p. 243).

The Normality of Attachment

Attachment was also proposed as an evolutionary basis upon which to consider abnormal psychological functioning. Allen and Badcock (2006) noted that "some [researchers], for example, have suggested that depression inhibits exploratory or risk-laden activities in the absence of secure attachment bonds, and instigates appeasement-related behaviors designed to maintain relationships (Gilbert, 2014). Others have argued that the depressive response serves as a distress call (Frijda, 1994), provokes a search for the lost relationship (Averill, 1968), or motivates the sufferer to avoid further deterioration of preexisting bonds (Ingram et al., 1998)" (p. 817).

The Normality of Social Risk and Fear of Exclusion

Extremes in social risk assessment and fear of social exclusion have also been proposed to account for abnormal psychological functioning. Gilbert (2001) noted that "If human social anxiety is not predominately about the fear of physical injury or attack, as it is in other animals, then, to understand human social anxiety (ie, fear of evaluation), it is necessary to consider why certain types of relationships are so important. Why do humans need to court the good feelings of others and fear not doing so? And why, when people wish to appear attractive to others (eg, to make friends, date a desired sexual partner, or give a good presentation), do some people become so overwhelmed with anxiety that they behave submissively and fearfully (which can be seen as unattractive) or are avoidant?" In his article entitled "Evolution and social anxiety: The role of attraction, social competition, and social hierarchies" (p. 723). Gilbert suggested "that humans have evolved to compete for attractiveness to make good impressions because these are related to eliciting important social resources and investments from others. These, in turn, have been linked to inclusive fitness and have physiological regulating effects. Being allocated a low social rank or [being] ostracized carries many negative consequences for controlling social resources and physiological regulation. Social anxiety, such as shame, [according to Gilbert] can be adaptive to the extent that it helps people to 'stay on track' with what is socially acceptable and what is not and could result in social sanction and exclusion. However, dysfunctional social anxiety is the result of activation of basic defensive mechanisms (and modules for) for threat detection and response (eg, inhibition, eye-gaze avoidance, flight, or submission) that can be recruited rapidly for dealing with immediate threats, override conscious wishes, and interfere with being seen as a 'useful associate'." Gilbert has also suggested that "socially anxious people are highly attuned to the competitive dynamics of trying to elicit approval and investment from others but that they perceive themselves to start from an inferior (ie, low-rank) position and, because of this, activate submissive defensives when attempting to present themselves as confident, able, and attractive to others. These submissive defences (which evolved to inhibit animals in low-rank positions from making claims on resources or up-rank bids) interfere with confident performance, leading to a failure cycle… If social anxiety (and disorders associated with it) are increasing in the modern age, one reason may be invigorated competition for social prestige, attractiveness, and resources" (p. 723).

Similarly, according to Bateson et al. (2011), "the function of the human anxiety response, and homologues in other species, is to prepare the individual to detect and deal with threats." Bateson also noted importantly that "a mechanism is working functionally in the evolutionary sense if it has a level of responsiveness that will, averaged across all individuals and the environments in which they live, maximize survival and reproduction. This is a very different criterion from those used to demarcate clinical boundaries in psychiatry, which are mainly based on level of suffering and quality of life. If a mechanism is producing distress or impairing quality of life, this does not necessarily mean that it is malfunctioning in the evolutionary sense. For many adaptations, such as the pain system, it is part of their design that they cause subjectively unpleasant states, and individuals' viability would be reduced if they did not do so under the appropriate circumstances. Thus, while undoubtedly some cases of anxiety disorder are pathological, in that the control mechanisms regulating the anxiety response have become dysregulated, it is also possible that some cases represent appropriate adaptive responses to the situation in which the person currently finds him or herself" (p. 708).

Normality?

There are no norms. All people are exceptions to a rule that doesn't exist.

Fernando Pessoa

Whatever the concept of normality may be, in psychology it is certainly a questionable concept with a somewhat questionable history. While it may be difficult to conceptualize or to find or agree on an acceptable or accurate definition, we can acknowledge with some degree of confidence that it is a concept that has often revealed our individual and collective arrogance and ignorance, and often shamefully our most prejudicial nature as a species. To acknowledge that it is a flexible concept is to acknowledge, in part, that it has been a fragile, unstable, and illusive one. Specifically, its perceived flexibility likely reveals much about our inability as a species to objectively model and measure our own behavior and to recognize our own biases in our attempts to do so. Its perceived flexibility is also likely to be a consequence of our often exaggerated, evaluative, context-blind interpretations of crude statistical means, medians, and modes of normally distributed population data. Importantly, normality's flexibility likely also reveals much about its evolution as a concept, from its dubious beginnings as the moral and ethical standard of a 19th-century eugenics-based class system to its multiple, more *sanitized* legal, educational, and psychiatric incarnations as the demarcation between what is socially acceptable and what is not.

Paradoxically, normality's flexibility as a psychological concept is probably most likely to be a consequence of its inherent tautological status, that is, our most accessible definition of the concept usually requires an invocation of an equally beguiling and perplexing concept: *abnormality*. Most notably, psychological expositions of normality, often articulated through a language of abnormality, have resulted in complex taxonomies of behavioral and cognitive pathology. These taxonomies have packaged human form and function in an attempt to distinguish healthy and adaptive behaviors and cognitions from those that are deemed unhealthy, maladaptive, and *diseased*. However, this packaging has been based on very broad assumptions that detectable biological and genetic markers ultimately underlie abnormal behavior and that said abnormality is biologically distinct from whatever remains. More often than not, however, this has rarely been shown to be the case, and in the absence of the necessary physiological and genetic evidence, we have been left in somewhat of a quandary. If much of that which we perceive and judge to be psychologically abnormal is chemically, anatomically, and genetically indistinct from that which we perceive and judge to be normal, then upon what do we attribute our discrimination?

In actuality, as a psychological construct "normality" (or rather our perception of it) probably most accurately and most simply reflects innate ethnocentrism. Rather than anything to do with stereotypically assumed variations in wellbeing or social conformity, much of what we believe to be normal, from a psychological perspective, is most likely an illusion, a by-product of our adaptive biases as a highly social species to perceive and to seek out difference. Perceived normality from this perspective is the most likely representation of reality for members of a species that possess the neural capacity to consider their own experiences/existence. Biases in care provision and care seeking, biases in intersexual and intrasexual attraction, competitive biases, reciprocal exchange biases, and in-group/out-group biases both maintain and enhance fitness but also, importantly, dictate functioning and frame cognition and emotion.

Our perception and recognition of what we perceive and believe to be normal therefore is informed directly by our reaction and attraction to what is safe, fit, and beneficial and our avoidance of what is harmful, dangerous, or unfamiliar. Our re-articulation of these perceptions as judgements of normality or abnormality, moreover, may simply reveal innate and extremely primitive preferences and biases communicated in a context of social norms and cultural beliefs. Importantly, therefore, our perception and recognition of what we perceive and believe to be psychologically abnormal too can be plausibly understood in this context of evolved and evolving bias.

REFERENCES

Allen, N.B., Badcock, P.B., 2006. Darwinian models of depression: a review of evolutionary accounts of mood and mood disorders. Progress in Neuro-Psychopharmacology and Biological Psychiatry 30 (5), 815–826.

American Psychiatric Association (APA), 1987. Diagnostic and Statistical Manual, third ed. revised. APA, Washington, DC.

Andrews, G., Henderson, S., Hall, W., 2001. Prevalence, comorbidity, disability and service utilisation overview of the Australian National Mental Health Survey. The British Journal of Psychiatry 178 (2), 145–153.

Averill, J.R., 1968. Grief: its nature and significance. Psychological Bulletin 70 (6), 721.

Axelrod, R., Hammond, R.A., April 2003. The evolution of ethnocentric behavior. In: Midwest Political Science Convention, pp. 2–30.

Bannister, D., 1968. The logical requirements of research into schizophrenia. The British Journal of Psychiatry 114 (507), 181–188 cited in Read, J., Mosher, L.R., Bentall, R.P., 2004. Models of madness: psychological, social and biological approaches to schizophrenia. Psychology Press.

Bartlett, S.J., 2011. Normality Does Not Equal Mental Health: The Need to Look Elsewhere for Good Standards of Good Psychological Health. Praeger, California.

Bateson, M., Brilot, B., Nettle, D., 2011. Anxiety: an evolutionary approach. Canadian Journal of Psychiatry 56 (12), 707–714.

Beck, A., 1962. Reliability of psychiatric diagnoses. American Journal of Psychiatry 119, 351–357.

Bentall, R.P., 2009. Doctoring the Mind: Why Psychiatric Treatments Fail. Penguin Books, London.

Carlson, N.R., 2010. Psychology the Science of Behaviour. Pearson, Canada.

Caspi, A., Houts, R.M., Belsky, D.W., Goldman-Mellor, S.J., Harrington, H., Israel, S., Moffitt, T.E., 2014. The p factor one general psychopathology factor in the structure of psychiatric disorders? Clinical Psychological Science 2 (2), 119–137.

Cooper, J.E., 1972. Psychiatric Diagnosis in New York and London: A Comparative Study of Mental Hospital Admissions.

Copeland, J.R.M., Cooper, J.E., Kendell, R.E., Gourlay, A.J., 1971. Differences in usage of diagnostic labels amongst psychiatrists in the British Isles. The British Journal of Psychiatry 118 (547), 629–640 cited in Read, J., Mosher, L.R., Bentall, R.P., 2004. Models of madness: psychological, social and biological approaches to schizophrenia. Psychology Press.

Copeland, W., Shanahan, L., Costello, E.J., Angold, A., 2011. Cumulative prevalence of psychiatric disorders by young adulthood: a prospective cohort analysis from the Great Smoky Mountains Study. Journal of the American Academy of Child and Adolescent Psychiatry 50, 252–261.

Costa Jr., P.T., McCrae, R.R., 1992. Revised NEO Personality Inventory (NEO-PI-R) and NEO Five-factor Inventory (NEO-FFI) Manual. Psychological Assessment Resources, Odessa, FL.

Davenport, C.B., 1911. Heredity in Relation to Eugenics, vol. 5. H. Holt cited in Whitaker, R., 2002. Mad in America: Bad Science, Bad Medicine, and the Enduring Mistreatment of the Mentally Ill. Basic Books.

Eysenck, H.J., Eysenck, S.B.G., 1976. Psychoticism as a Dimension of Personality. Hodder & Stoughton, London.

Fleming, S., Shevlin, M., Murphy, J., Joseph, S., 2014. Psychosis within dimensional and categorical models of mental illness. Psychosis 6 (1), 4–15.

Forbush, K.T., Watson, D., 2013. The structure of common and uncommon mental disorders. Psychological Medicine 43, 97–108.

Frances, A., 2013. Saving Normal: An Insider's Revolt against Out-of-control Psychiatric Diagnosis, DSM-5, Big Pharma, and the Medicalization of Ordinary Life. Harper Collins Publishers.

Frijda, N.H., 1994. Emotions are functional, most of the time. The Nature of Emotions: Fundamental Questions 197–202.

Galton, F., 1869. Hereditary Genius. Macmillan and Company.

Gilbert, P., 1998. Evolutionary psychopathology: why isn't the mind designed better than it is? British Journal of Medical Psychology 71 (4), 353–373.

Gilbert, P., 2001. Evolution and social anxiety: the role of attraction, social competition, and social hierarchies. Psychiatric Clinics of North America 24 (4), 723–751.

Gilbert, P., 2014. Depression: The Evolution of Powerlessness. Psychology Press.

Goffman, E., 1968. Asylums: Essays on the Social Situation of Mental Patients and Other Inmates. Aldine Transaction.

Grob, G.N., 1991. Origins of DSM-I: a study in appearance and reality. American Journal of Psychiatry 148 (4), 421–431 cited in Whitaker, R., Cosgrove, L., 2015. Psychiatry under the influence: Institutional corruption, social injury, and prescriptions for reform. Palgrave MacMillan.

Harvard School of Medicine, 2005. National Comorbidity Survey-Replication. http://www.hcp.med.harvard.edu/ncs/.

Hasin, D., Kilcoyne, B., 2012. Comorbidity of psychiatric and substance use disorders in the United States: current issues and findings from the NESARC. Current Opinion in Psychiatry 25, 165–171.

Hoffman, D.D., 2012. The construction of visual reality. In: Hallucinations. Springer, New York, pp. 7–15.

Ingram, R.E., Miranda, J., Segal, Z.V., 1998. Cognitive Vulnerability to Depression. Guilford Press.

Jacobi, F., Wittchen, H.U., Hölting, C., Höfler, M., Pfister, H., Müller, N., Lieb, R., 2004. Prevalence, co-morbidity and correlates of mental disorders in the general population: results from the German Health Interview and Examination Survey (GHS). Psychological Medicine 34 (04), 597–611.

Kelleher, I., Jenner, J.A., Cannon, M., 2010. Psychotic symptoms in the general population–an evolutionary perspective. The British Journal of Psychiatry 197 (3), 167–169.

Kendler, K.S., Prescott, C.A., Myers, J., Neale, M.C., 2003. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. Archives of General Psychiatry 60, 929–937.

Kotov, R., Chang, S.W., Fochtmann, L.J., Mojtabai, R., Carlson, G.A., Sedler, M.J., Bromet, E.J., 2010. Schizophrenia in the internalizing-externalizing framework: a third dimension? Schizophrenia Bulletin 37, 1168–1178.

Kotov, R., Ruggero, C.J., Krueger, R.F., Watson, D., Yuan, Q., Zimmerman, M., 2011. New dimensions in the quantitative classification of mental illness. Archives of General Psychiatry 68, 1003–1011.

Krueger, R.F., Markon, K.E., 2011. A dimensional-spectrum model of psychopathology: progress and opportunities. Archives of General Psychiatry 68, 10–11.

Krueger, R.F., Caspi, A., Moffitt, T.E., Silva, P.A., 1998. The structure and stability of common mental disorders (DSM III-R): a longitudinal-epidemiological study. Journal of Abnormal Psychology 107, 216–227.

Leahy, R.L., 1997. Depression and resistance: an investment model of decision-making. Behaviour Therapist 20, 3–5.

Moffitt, T.E., Arseneault, L., Belsky, D., Dickson, N., Hancox, R.J., Harrington, H., Caspi, A., 2011. A gradient of childhood self-control predicts health, wealth, and public safety. Proceedings of the National Academy of Sciences of the United States of America 108, 2693–2698.

Moller, L.R., Sorensen, M.J., Thomsen, P.H., 2007. ICD-10 classification in Danish child and adolescent psychiatry – have diagnoses changed after the introduction of ICD-10? Nordic Journal of Psychiatry 61, 71–78.

Munk-Jorgensen, P., Najarraq, L.M., Bertelsen, A., 2010. Use of ICD-10 diagnoses in Danish psychiatric hospital-based services in 2001–2007. World Psychiatry 9, 183–184.

Murphy, J., Shevlin, M., Adamson, G., Houston, J., 2009. Positive psychosis symptom structure in the general population: assessing dimensional consistency and continuity from 'pathology' to 'normality'. Psychosis: Psychological, Social and Integrative Approaches 2, 199–209.

Murphy, J., Shevlin, M., Houston, J., Adamson, G., 2012. A population based analysis of subclinical psychosis and help-seeking behavior. Schizophrenia Bulletin 38, 360–367.

Nesse, R.M., 2000. Is depression an adaptation? Archives of General Psychiatry 57 (1), 14–20.

Nesse, R.M., 2004. Cliff-edged fitness functions and the persistence of schizophrenia. Behavioral and Brain Sciences 27 (06), 862–863.

Nettle, D., Bateson, M., 2012. The evolutionary origins of mood and its disorders. Current Biology 22 (17), R712–R721.

Newman, D.L., Moffitt, T.E., Caspi, A., Magdol, L., Silva, P.A., Stanton, W.R., 1996. Psychiatric disorder in a birth cohort of young adults: prevalence, comorbidity, clinical significance, and new case incidence from ages 11 to 21. Journal of Consulting and Clinical Psychology 64 (3), 552.

Ottati, V., Bodenhausen, G.V., Newman, L.S., 2005. Social psychological models of mental illness stigma. On the Stigma of Mental Illness: Practical Strategies for Research and Social Change 99–128.

Pratto, F., Sidanius, J., Stallworth, L.M., Malle, B.F., 1994. Social dominance orientation: a personality variable predicting social and political attitudes. Journal of Personality and Social Psychology 67 (4), 741.

Price, J., 1967. The dominance hierarchy and the evolution of mental illness. The Lancet 290 (7509), 243–246.

Read, J., Harré, N., 2001. The role of biological and genetic causal beliefs in the stigmatisation of 'mental patients'. Journal of Mental Health 10 (2), 223–235.

Read, J., Mosher, L.R., Bentall, R.P., 2004. Models of Madness: Psychological, Social and Biological Approaches to Schizophrenia. Psychology Press.

Read, J., Haslam, N., Sayce, L., Davies, E., 2006. Prejudice and schizophrenia: a review of the 'mental illness is an illness like any other' approach. Acta Psychiatrica Scandinavica 114 (5), 303–318.

Rosanoff, A.J., Orr, F.I., 1911. A study of heredity in insanity in the light of the Mendelian theory. American Journal of Psychiatry 68 (2), 221–261 cited in Whitaker, R., 2002. Mad in America: Bad Science, Bad Medicine, and the Enduring Mistreatment of the Mentally Ill. Basic Books.

Rosenhan, D.L., 1973. On being sane in insane places. Science 179 (4070), 250–258.

Seligman, M.E., 1975. Helplessness: On Depression, Development, and Death. WH Freeman/Times Books/Henry Holt & Co.

Szasz, T.S., 1960. The myth of mental illness. American Psychologist 15 (2), 113.

Uher, R., Rutter, M., 2012. Basing psychiatric classification on scientific foundation: problems and prospects. International Review of Psychiatry 24 (6), 591–605.

van den Berghe, P., 1996. Does race matter? In: Hutchinson, J., Smith, A.D. (Eds.), Ethnicity. Oxford University Press, Oxford.

van den Dennen, J., 1987. Ethnocentrism and in-group/out-group differentiation. The Sociobiology of Ethnocentrism (London), p. 1–47.

van Os, J., Linscott, R.J., Myin-Germeys, I., Delespaul, P., Krabbendam, L., 2009. A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. Psychological Medicine 39, 179–195.

Watson, A.C., Ottati, V., Corrigan, P., 2003. From whence comes mental illness stigma? International Journal of Social Psychiatry 49 (2), 142–157.

Whitaker, R., Cosgrove, L., 2015. Psychiatry Under the Influence: Institutional Corruption, Social Injury, and Prescriptions for Reform. Palgrave MacMillan.

Whitaker, R., 2002. Mad in America: Bad Science, Bad Medicine, and the Enduring Mistreatment of the Mentally Ill. Basic Books.

Chapter 28

Diversity and Hierarchy in the Evolution of Mental Mechanisms

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INTRODUCTION

Readers of a volume about human nature might be surprised to discover not only that there remains enormous controversy over what human nature is, but also about whether it even exists. Well into the 21st century, philosophers, biologists, anthropologists, and others continue to call into question the very idea that there is something, anything, that makes humans human (Buller, 2005; Downes and Machery, 2013; Ehrlich, 2000; Hull, 1986; Ingold, 2006; Richerson, 2015). Certainly, the concept itself is ancient, well predating modern science, and therefore perhaps it is time for it to be retired. Is there anything about the concept of human nature worth keeping?

On the one hand, there is much about folk concepts of human nature that is probably wrong. Essentialist notions of human nature, for example, hold that the identity of members of a species is tied to some invariant, unchanging, underlying "essence." As biologists, psychologists, and philosophers have pointed out, essentialist thinking might be a useful heuristic for navigating a world of natural kinds, but it cannot be scientifically correct (Hull, 1986; Mayr, 1963). That is, while it might be useful for us to think of a sparrow as being a variant of the same underlying type as other sparrows, there is not *in fact* an underlying, universal, and unchangeable essence that makes a sparrow a sparrow (Barrett, 2001; Gelman, 2003). Even particular DNA sequences will not do: many members of a given species, such as humans, carry rare mutations in genes that most of the species carry, and yet they are still human. Moreover, the genome changes over time, with some regions changing rapidly because of arms races against diseases, the spread of agriculture, and other environmental changes; surely this does not mean that we are now a different species than we were a few thousand years ago.

On the other hand, discarding altogether the idea of a human nature of some kind might be going too far. After all, even biologists, while aware of the problems of essentialism, are able to refer to biological species and other taxa typically without undue difficulty. A primatologist, for example, might describe himself as a specialist in chimpanzee behavior without excessive anxiety about whether or not chimpanzee behavior, as an object of study, exists. Similarly, it seems we should have a notion of human nature that recognizes that people can study human behavior, the human brain, and the human capacity for culture without those terms being semantically empty.

Any scientific notion of human nature, however, must be *biologically correct.* To the extent that folk concepts of human nature are flawed, we should explicitly avoid them in constructing a scientifically valid notion of human nature. Moreover, any notion of human nature that we wish to endorse scientifically must grapple with the messy complexities of those biological clouds of organisms we call species. In particular, it must confront the facts of descent with modification, which leads to distributions of traits within and across taxa that defy simple ideas of each species having a unique, *sui generis* nature.

Here, I will focus in particular on the human brain and behavior, and I will explore what careful biological thinking might tell us about human *psychological* nature. What I will suggest is that the human brain and mind are likely to be a complex evolutionary mosaic of parts and processes with diverse evolutionary histories and relationships between them. Recent human evolution has been, of course, a process of genetic and developmental tinkering with the brain that was present in the chimpanzee-human common ancestor. This implies, as is the case for all phenotypes, that the human brain is a complex mix of ancient

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00028-4

and derived traits without a single simple linear pathway describing their evolution. Recognizing the implications of this will help us to better understand human nature, whatever it might ultimately prove to be.

EVO-DEVO AND DESCENT WITH MODIFICATION IN THE BRAIN

When the high degree of genetic similarity between humans and chimpanzees was first revealed, many commentators assumed that the implications for human nature were stark. If human nature is equated with uniquely derived characteristics in the human lineage, then the massive genetic overlap between humans and chimpanzees suggests that human nature must be tiny indeed. For brain architecture, the two main choices appeared to be either that the main innovation in human brains was an increase in size—an ape brain inflated—or that there were a small number of brain mechanisms, which, when added to an ape brain, produced human behavior: mechanisms of language, for example, or cultural learning.

A more careful look at the ways in which evolutionary change occurs in complex organisms suggests that these are not the only two options. Research in evolutionary developmental biology (evo-devo) suggests that much evolutionary change occurs through modification in the regulatory systems that build developing organisms, leading to evolutionary changes in phenotypes and associated functional properties that can be both disproportional to the overall amount of genetic changes and mosaic in nature, with different types and amount of change for different aspects of the phenotype (Carroll et al., 2005). Comparative work on brain development, architecture, and genomics suggests that this nonlinear, mosaic picture of brain evolution applies within the brain as well. Mammalian brains evolve, as do the rest of our bodies, through descent with modification of the brains of our ancestors. However, the genetic regulatory systems that control brain development are complex, orchestrating cascades of fine-grained morphological differentiation across space and time as the brain develops, in interaction with internal crosstalk and external inputs (Krubitzer and Huffman, 2000). Tweaking of the developmental knobs of these systems can allow, in principle, for many more finely grained evolutionary changes than either the "inflated ape brain" or the "ape brain plus extra modules" views imply. And there is empirical evidence that evolutionary changes in the human brain have indeed occurred in a mosaic fashion, as has the evolution of mammalian brains more generally (Barton and Harvey, 2000; Preuss, 2004; Striedter, 2005).

The move to an evolutionary developmental view of human brain evolution has implications for how we think of the organization and evolved design of human psychology, as well as for how we think about human nature. Most basically, because the brain develops during ontogeny via a process of serial differentiation and specialization of tissues, evolutionary change occurs via modification of these developmental processes. This means that both brain development and brain evolution are likely to show a hierarchical pattern in which brain structures are related to each other through processes of descent with modification. The brain is a mix of ancient and newer structures, with the new derived from, and drawing on the functional properties of, the old. In structures such as the cortex—of particular interest for so-called "higher" cognitive faculties—relationships of homology from common ancestral structures suggest that there are likely to be widely shared properties of functional organization, with subspecializations nested within these shared properties. As elsewhere in biology, "new" brain functions are thus likely to evolve from older ones via descent with modification, and thus to share large amounts of basic functional organization, modified either phylogenetically or ontogenetically, or both, for specific tasks, some of which may be novel in humans (eg, language, cooperation, tool use). This hierarchical view of brain organization diverges sharply from older, classically "modular" views of brain architecture, and it paints a different picture of human nature as well (Barrett, 2012).

CLASSICAL VERSUS HIERARCHICAL MODULARITY

The classical view of modularity, associated most closely with philosopher Jerry Fodor's book, *The Modularity of Mind* (1983), divides brain mechanisms into two types, modular and non-modular (or "peripheral" and "central," in Fodor's formulation). Cognitive modules, in this view, are narrow, isolated, reflex-like information processors, characterized by a checklist of features including domain specificity, informational encapsulation, obligatory firing, fast speed, shallow outputs, limited accessibility, characteristic ontogeny, and fixed neural architecture. In contrast, non-modular processes were deemed by Fodor to be open-ended, general-purpose, and lacking internal structure.

From a biological point of view, however, there is no reason to suppose either that the brain consists of a strict two-layer architecture, nor that functional "modules" need consist only of reflex-like peripheral systems in perception and motor control. Instead, mounting evidence from neuroscience supports a model of complex cognition as resulting from the orchestration of complex assemblages of networks that are modular at multiple levels, with smaller modular units nested within larger ones (Meunier et al., 2009). Functionally specialized cognition, in this view, emerges from coordinated division of labor between many

specialized processes, but these processes are neither fully isolated from each other, as the classical view would have it, nor simply automatic reflexes that operate identically independently of context.

Evolutionarily, the neocortex of mammals appears to have evolved through successive expansion and functional sub-differentiation from the smaller and simpler cortex of ancestral reptiles (Kaas, 2006). This suggests that different mechanisms and regions of the human cortex are likely to exhibit hierarchical patterns of properties, with many basic developmental and computational properties shared across the entire cortex, but with differences in fine-tuning in different cortical areas as a result of both descent with modification as well as differences in inputs to these regions during development (Barrett, 2012). It makes sense that at one level the cortex acts as a unit, in that complex cognitive processes entail patterns of activation across the cortex in combination with subcortical structures, but that this large-scale activity reflects orchestrated division of labor between many functionally differentiated subprocesses. In this sense, large-scale cognitive activity in the brain is hierarchical in nature (Bullmore and Sporns, 2009).

What "diversity" means in this context is that the brain is composed of many types of mechanisms, with diverse functions and evolutionary histories. What "hierarchy" means is that many of these mechanisms are likely related to each other through patterns of descent with modification, that is, homology. As brains increased in size in primates, apes, and the hominin lineages, expansion of the brain led to increasing complexity through several routes, including sub-differentiation of cortical regions, partial reorganization of existing brain structures and, perhaps, the evolution of some genuinely new structures and connections (Allman, 2000; Kaas, 2000; Preuss, 2004; Striedter, 2005). However, because newer mechanisms evolve from older ones, even derived structures in human brains inherit much of the functional architecture of older structures, modified for new purposes, and they can participate in processing cascades in which newer and older mechanisms interact through computational division of labor.

Central to the hierarchical view of human brain architecture is the tension, present everywhere in evolution, between what is old and what is new. At some level, all features of the brain derive from the ancient nervous systems of our vertebrate ancestors and so, if one goes far back enough, all structures and mechanisms in the brain are homologous at a deep level, and brain mechanisms across vertebrates exhibit relationships of homology as well (though untangling the exact nature of these homologies is not trivial; Striedter and Northcutt, 1991). However, if one is interested in uniquely derived features of the human lineage—autapomorphies—then one must examine not just relationships of homology, or descent, but patterns of modification, or derived features, as well. Everything new is a modified version of something old. Hence, while humans undoubtedly possess many unique psychological capacities, such as spoken language, large-scale cooperation, and sophisticated skills of cultural transmission, every one of these is based on some combination of brain mechanisms that are modifications of older mechanisms present in other primates.

With the advent of methods for fine-grained mapping of the genome and patterns of gene expression during development, we are beginning to get a glimpse of the modifications in genes and genetic regulatory elements that have produced the modified homologies we see in the human brain, and that support uniquely human aspects of cognition and behavior (Cáceres et al., 2003; Enard et al., 2002). We are still only at the beginning of a long pathway to understanding exactly how differences in gene sequences produce the psychological and behavioral differences in phenotype we observe between humans and the other great apes. However, the hierarchical view of brain evolution carries several important implications for how we theorize human nature, scientifically.

MOST OF HUMAN NATURE IS NOT HUMAN SPECIFIC

It might seem natural to treat all and only uniquely derived features in humans, or autapomorphies, as the sum total of human nature. This approach, however, raises at least two problems. First, it is difficult to shave off just the unique bits, built as they are on top of shared homologies. For example, while much of uniquely human cognition probably derives from modifications to the cortex, this does not necessarily mean genuinely new cortical regions; indeed, there is little or no evidence for major new brain regions in humans (Preuss, 2004). However, while it is perhaps surprising that our uniquely derived cognitive abilities, such as language, appear to depend on brain regions and networks that are homologous to those present in other primates, this does not preclude the possibility of substantial reorganization and partial repurposing of brain structures. For example, while it appears that Broca's area, crucial for speech in humans, is homologous with cortical areas 44 and 45 in nonhuman primates, it is likely that evolutionary changes occurred both within the region itself and in its connections with other brain networks in the evolution of human speech (Preuss, 2000; Rizzolatti and Arbib, 1998; Striedter, 2005). Certainly, this implies that there must be uniquely derived *features* of these areas in humans, but language abilities presumably depend on aspects of these brain regions that are not unique to humans. Moreover, new cognitive abilities may sometimes come from partial ontogenetic repurposing of cortical areas present in other primates (Anderson, 2010).

Second, even if we could partition off just the uniquely derived features of humans, it is not clear that a concept of human nature based only on these features would serve the purposes for which such a concept is typically invoked. Take, for example, kinship and parental care, two frequently cited human universals (Brown, 1991). While there is substantial cultural diversity in how kinship is organized, most anthropologists would agree that kinship and family relationships are central to the organization of all human societies (Chapais, 2009). And yet, kinship itself is of course not unique to humans, nor is parental care. *Aspects* of kinship and parental care, including the importance of extended families and biparental care (care of offspring by both the mother and the father), might be unique to humans. But who would want to say that a father's love of his children, perhaps uniquely derived in humans, is part of human nature, while a mother's love of her children, shared with other primates, is not?

A phylogenetic view of species allows us to say with confidence that humans, chimpanzees, bonobos, gorillas, and orangutans are different biological species, because they are now distinct lineages. Thus, there is a gorilla nature, a human nature, and so on. The phylogenetic method also allows us, in some cases, to determine which traits are uniquely derived in each lineage. However, the facts of homology suggest that the "nature" of each species includes many elements that predate its separation from other lineages. Gorilla nature and human nature heavily overlap. So do human nature and mouse nature, and even, for some purposes, human nature and fish nature. Maternal care of offspring, for example, is a mammalian trait, and therefore part of the nature of all primates. Similarly, many aspects of our health and physiology are shared with other apes, other mammals, and beyond (Natterson-Horowitz and Bowers, 2012). Psychologically, the same is undoubtedly true. For example, many human emotions, such as fear, are not uniquely human. While these emotions might have been modified and manifest themselves in unique ways in humans, emotional responses involve the complex interplay between many mechanisms, including phylogenetically old ones, and it would be functionally odd to partition off just the human parts.

MUCH OF HUMAN UNIQUENESS ARISES IN PART FROM NON-UNIQUELY HUMAN MECHANISMS

The facts of homology suggest that even aspects of humans that might be uniquely derived probably depend heavily on aspects that are not. This is simply a fact of the interactive nature of functional wholes. To use an analogy from technology, technological advancements such as the jet engine that were called "new" when they appeared nevertheless make use of many older technologies in their operation, and so are not entirely new. Similarly, while it is unclear whether humans possess any completely new brain regions relative to other apes or monkeys, there is evidence that homologous brain regions have been modified in humans relative to our ancestors. Moreover, there is evidence that brain modifications in humans have occurred differentially across different brain regions, and that they are not, as is commonly assumed, restricted merely to the neocortex or even more narrowly to the frontal cortex. For example, humans appear to have derived modifications in the architecture of one of the layers of primary visual cortex, V1, one of the more phylogenetically ancient areas of mammalian cortex (Preuss, 2004). These modifications in V1 do not mean, of course, that our vision operates in entirely different ways that the vision of, for example, macaques. Instead, human vision is likely to make use of principles of neural organization and computation that are phylogenetically widespread, but that exhibit some unique modifications in our lineage. Instead of thinking of modular architectures as fixed and composed of unchanging, non-interactive elements, it is better to think of them as composed of functional parts that can be tweaked and rearranged to produce new computational designs out of older parts.

The same point—that new cognitive abilities come from making evolutionary modifications within hierarchies of existing parts— is likely to be true even for abilities that seem qualitatively different from those seen in other species, such as human abilities of social cognition. Some social skills in humans, such as "mindreading," the ability to make inferences about the mental states of others, seem so far removed even from chimpanzees that some scholars have claimed that the difference challenges the very idea of interspecies psychological continuity (Penn et al., 2008). However, just as visual perception involves the hierarchical interaction of multiple mechanisms, some old and some new, social perception is likely to as well. Simple forms of mindreading, such as the use of gaze to make predictive decisions about how to respond to the behavior of other organisms, are phylogenetically widespread (Emery, 2000). Human mindreading, too, makes heavy use of gaze perception, as well as perception of posture, body movement, and other low-level cues (Johnson and Shiffrar, 2013). There is every reason to think that phylogenetically ancient mechanisms of social perception, such as gaze and motion perception, have homologs in humans that have been evolutionarily preserved, though perhaps in modified form, and that participate in a hierarchical fashion in more sophisticated forms of mindreading, such as tracking false beliefs.

Indeed, "higher level" forms of mindreading, such as tracking other individuals' intentions and knowledge states, have been found to exist in other social taxa such as

corvids, canids, and apes (Clayton et al., 2007; Hare et al., 2001, 2002). While some of these cases might represent cases of convergent evolution—for example, corvids and canids—others, in particular apes, probably represent cases of mechanisms that are homologous with those seen in humans. Indeed, the only form of higher level mindreading for which evidence remains categorically absent in any other species than humans is the tracking of *false* beliefs (Call and Tomasello, 2008).

Sophisticated and apparently uniquely derived cognitive abilities in humans, then, probably make extensive use of more basic and more phylogenetically widespread mechanisms that are still present in humans. What appears to be a single, seamless ability such as the ability to track and make inferences based on another's false beliefs about the world is likely to be the result of multiple mechanisms interacting, some old and some new. For example, versions of the false belief task (Wellman et al., 2001) that require inferring an agent's false representation of the location of an object usually make use of mechanisms for computing what an agent has or has not seen, which are probably present across primates, and perhaps even more widely (Emery, 2000). However, this does not mean that any other species than humans, so far as we know, can compute an individual's false belief about an object's location based on computing what the agent has previously seen, even though the latter computation, itself, is something of which other species are capable. Thus, the uniquely human ability to form a representation of an agent's false belief based on what the agent has seen depends on mechanisms that are not uniquely human, such as gaze tracking.

Most complex cognitive tasks probably make use of hierarchical cascades of mechanisms, building up complex representations and inferences from simpler ones. If so, there may be many complex skills whose sum total is unique to humans, but for which most of the participating components are not. This is likely to be true of many uniquely human abilities, including mindreading, language processing, large-scale cooperation, moral cognition, and cultural transmission (Barrett, 2015).

PART OF HUMAN UNIQUENESS MUST LIE IN UNIQUELY MODIFIED INTERACTIONS

The most intuitive source of evolutionary innovation in a species is the addition of new mechanisms or modification of older mechanisms to give them new properties. But as the example of gaze processing in false belief tracking shows, new cognitive skills can be produced in part through the modification of interactions between mechanisms, including mechanisms that already existed. The ability to create and manipulate tools, for example, probably makes use at least in part of visual and motor abilities that are present in other species. Indeed, both observation and execution of tool use in humans recruit brain areas with homologies in nonhuman primates, including regions of temporal, parietal, and premotor cortex (Johnson-Frey, 2004). However, human capacities to conceptualize, manufacture, and learn about tools appear to differ from those of even of our closest primate relatives in several ways, including our abilities to conceptualize tool functions, to rapidly infer the intentions and goals of those using tools, and to quickly acquire culturally normative tool conventions (Csibra and Gergely, 2009; German and Barrett, 2005; Kemler-Nelson et al., 2000; Lyons et al., 2007; Povinelli, 2000; Rakoczy and Schmidt, 2013). Thus, human tool use seems to draw heavily on capacities and brain mechanisms present in nonhuman primates, but the behavioral data suggest that these capacities must have been modified and/or recombined in unique ways to produce our uniquely human abilities of artifact cognition.

As already mentioned, human language abilities, while unique to humans, appear to make use of brain areas that are not unique to humans (Preuss, 2000). However, human language abilities are not the result of activity in a single brain region, but rather, involve interactions between perception, motor, and conceptual areas of the brain. The evolution of language, then, might have involved not just modifications to regions such as Broca's area, but modified interactions between brain areas, creating new computational synergies that were not present before. Consistent with this, it appears that white matter pathways involved in human language abilities have been expanded in the human lineage. A particular white matter pathway, the arcuate fasciculus, appears to have evolved projections in humans that link regions involved in lexical-semantic and syntactic processing, perhaps creating new processing connections between areas that existed, but were not similarly connected, in other primates (Rilling et al., 2008).

Of course, the creation of new pathways of interaction between brain regions can modify those regions both ontogenetically, due to the plastic nature of cortical development, but also over evolutionary time, as new connections will generate phenotypic variation between individuals in psychological capacities that can then be further acted on by selection. Research on reading in the brain provides a provocative example of how cortical tissue can take on new functions given novel but regular input and consistent task demands, suggesting that the addition of changes in human environments—including social and cultural environments—might provide knock-on effects to changes in brain size and wiring patterns, leading to radically new phenotypic outcomes (Dehaene, 2009).

EVOLUTIONARY FEEDBACK AS A MISSING INGREDIENT

It is commonly acknowledged that a description of the environment in which adaptations evolved (their EEA, or environment of evolutionary adaptedness) is crucial for understanding why adaptations take the form they do, and that both environment and genes matter in determining how phenotypes develop. However, it is becoming increasingly clear that the bidirectional nature of evolutionary causation, with changes in phenotypes leading to changes in the environment and vice-versa, has been particularly important in human evolution (Laland et al., 2001; Richerson and Boyd, 2005). Evolutionary feedback cascades of this kind are likely to have been important in the evolution of social intelligence, language, artifacts, and mechanisms of cultural transmission. In each case, gradual changes in cognitive capacities in turn changed the environment of selection in a positive self-feeding loop. Runaway processes such as this were likely important in the rapid expansion in brain size seen in the genus *Homo,* and in modifications to brain regions involved in language, tool use, and social cognition. Thus, a complete understanding of human nature requires an understanding of how humans modified their own environments of selection in ways that have left their signatures on modern brains and behavior.

The evolution of tool use, and of human-made artifacts more generally, provides a good case study of how evolutionary feedback has shaped human nature. Because modern-day chimpanzees and humans both manufacture and use tools (as do some other nonhuman primates as well), it is likely that the common ancestor of chimps and humans did too. Thus, as for mindreading, it is likely that human artifact cognition evolved through modification of evolutionarily older mechanisms that are not unique to our lineage. However, artifact cognition in nonhuman primates is profoundly different from that of humans in several ways. For one, the complexity and diversity of tools made by nonhuman primates are orders of magnitude lower than those made by humans; we make computers; they make termite-fishing sticks. Second, the processes of cultural transmission of tool use in nonhuman primates are quite different than in humans: for example, capuchin monkeys can learn to use stones to crack nuts, but the skill can take years to learn, and is acquired via a painfully slow trial-and-error process (Dindo et al., 2008). Third, the complexity of human artifacts themselves evolves via a ratcheting process of cultural evolution, something that is not known to occur for the artifacts of any other species (Tennie et al., 2009).

What these facts suggest is that at some point in human evolutionary history, probably after humans began to modify stone tools by flaking, a positive evolutionary feedback loop began in which increasingly sophisticated tools led to accelerating fitness benefits, exerting strong selection on brain regions involved in learning to make and use tools. These included regions involved in both conceptualizing tools, and in producing and using them, each of which in turn involves multiple subprocesses (Johnson-Frey, 2004). Conceptual knowledge of tools involves not only recognition and naming of the tool, but also knowledge of its functions and associated actions. From early childhood, human learning about artifacts appears categorically different from that of other primates. Apes, for example, seem to learn about tools largely through their affordances, whereas children early on classify tools based on their culturally normative proper function (Kemler Nelson et al., 2000). Corollaries of this include "functional fixedness," in which humans have difficulty conceptualizing uses for a tool other than that for which it was designed (German and Barrett, 2005), and "over-imitation," in which humans, but not other primates, consistently copy others' intentional actions with respect to tools even when these actions have no instrumental function (Lyons et al., 2007). These phenomena suggest that for humans, tools are a fundamentally different kind of thing than they are for other primates: a special category of object classified by function, and tied to specific motor routines for use. In addition, the ability of humans to represent and make extremely complex artifacts, with multiple functional parts, suggested that the mechanisms that represent artifacts in the brain must have undergone modifications of some kind as well.

Although the earliest human-made artifacts were handheld tools, increasing complexity of human capacities to conceptualize and manufacture functional artifacts led to the evolution of new kinds of human-made object such as clothing, shelter, body ornamentation, and later vehicles, roads, and other features of the built environment. Clearly, these changes altered human environments in ways that fed back on our own biology: for example, changes in clothing, shelter, energy processing and food technology led to peopling of regions of the globe that would otherwise have been inaccessible to savanna-dwelling apes. Research on how literacy alters brain architecture provides a good example of how a particular kind of human-made artifact, writing, profoundly alters human physical and social environments in ways that alter the development of cognition and the brain (Dehaene, 2009). Similarly, there is evidence that changes in human food technologies associated with artifact use, such as cooking, dairying, and agriculture, have altered the human genome (Hardy et al., 2015; Perry et al., 2007; Tishkoff et al., 2007). In this sense, then, human nature is partly the product of humans themselves. We are currently only beginning to understand the nature of the self-feeding evolutionary cascades that have resulted in human dominance of the globe, and our anthropogenic influence on it (Steffen et al., 2007). Exploring such feedback processes, including those involved in the evolution of

language, cultural transmission, and large-scale social organization, will be necessary for a complete understanding of human nature.

CONCLUSION

Human nature is not monolithic. While humans do have distinguishing psychological and behavioral traits such as language, the ability to cooperate in large social groups, and tool use, each of these is the product of many interacting mechanisms within the brain, some phylogenetically old and some new. As brain size increased in the hominin lineage, particularly in our genus, *Homo,* it is likely that brain complexity increased as well. While expansion in brain size undoubtedly increased the behavioral repertoire in humans—presumably leading to the fitness advantages that outweighed the metabolic and developmental costs of larger brains—the added behavioral complexity afforded by large brains did not simply appear de novo, but rather through the modification and elaboration of previously existing brain mechanisms and regions. Thus, human nature is built out of, and rests upon, a foundation of phylogenetically older mechanisms. Human nature is nested within ape nature, which is nested within primate nature, mammal nature, vertebrate nature, and so on.

What this means is that the search for human nature should embrace the parts of us—the majority of our parts, in fact—that are not exclusively human. Our most mundane daily activities, such as conversation, both draw upon abilities that no other species possesses, such as the ability to parse grammatical constructions, and upon abilities that are not unique to us, such as sensitivity to others' emotional signals. It is not in individual psychological mechanisms that human nature is to be found, but in how the operation of these mechanisms is combined uniquely in us. The search for human nature, then, should embrace the idea of a multi-modular mind: one that is likely to have evolved in a complex series of modifications, each of which might have been modest in itself, but which interacted to produce the enormous changes in cognition and behavior that have enabled us to become, for better or worse, one of the most successful species on earth.

REFERENCES

Allman, J.M., 2000. Evolving Brains. Scientific American Library, New York, NY.

Anderson, M.L., 2010. Neural reuse: a fundamental organizational principle of the brain. Behavioral and Brain Sciences 33, 245–266.

Barrett, H.C., 2001. On the functional origins of essentialism. Mind and Society 3, 1–30.

Barrett, H.C., 2012. A hierarchical model of the evolution of human brain specializations. Proceedings of the National Academy of Sciences of the United States of America 109, 10733–10740.

Barrett, H.C., 2015. The Shape of Thought: How Mental Adaptations Evolve. Oxford University Press, New York, NY.

Barton, R.A., Harvey, P.H., 2000. Mosaic evolution of brain structure in mammals. Nature 405, 1055–1058.

Brown, D.E., 1991. Human Universals. McGraw-Hill, New York, NY.

Buller, D., 2005. Adapting Minds: Evolutionary Psychology and the Persistent Quest for Human Nature. MIT Press, Cambridge, MA.

Bullmore, E., Sporns, O., 2009. Complex brain networks: graph theoretical analysis of structural and functional systems. Nature Reviews Neuroscience 10, 186–198.

Cáceres, M., Lachuer, J., Zapala, M.A., Redmond, J.C., Kudo, L., Geschwind, D.H., Lockhart, D.J., Preuss, T.M., Barlow, C., 2003. Elevated gene expression levels distinguish human from non-human primate brains. Proceedings of the National Academy of Sciences of the United States of America 100, 13030–13035.

Call, J., Tomasello, M., 2008. Does the chimpanzee have a theory of mind? 30 years later. Trends in Cognitive Sciences 12, 187–192.

Carroll, S.B., Grenier, J.K., Weatherbee, S.D., 2005. From DNA to Diversity: Molecular Genetics and the Evolution of Animal Design, second ed. Blackwell, Oxford, UK.

Chapais, B., 2009. Primeval Kinship: How Pair-bonding Gave Birth to Human Society. Harvard University Press, Cambridge, MA.

Clayton, N.S., Dally, J.M., Emery, N.J., 2007. Social cognition by food-caching corvids: the western scrub-jay as a natural psychologist. Philosophical Transactions of the Royal Society B: Biological Sciences 362, 507–522.

Csibra, G., Gergely, G., 2009. Natural pedagogy. Trends in Cognitive Sciences 13, 148–153.

Dehaene, S., 2009. Reading in the Brain: The Science and Evolution of a Human Invention. Viking, New York, NY.

Dindo, M., Thierry, B., Whiten, A., 2008. Social diffusion of novel foraging methods in brown capuchin monkeys (*Cebus apella*). Proceedings of the Royal Society B: Biological Sciences 275, 187–193.

Downes, S.M., Machery, E., 2013. Arguing About Human Nature: Contemporary Debates. Routledge, New York.

Ehrlich, P.R., 2000. Human Natures: Genes, Cultures, and the Human Prospect. Island Press, Washington, DC.

Emery, N.J., 2000. The eyes have it: the neuroethology, function and evolution of social gaze. Neuroscience & Biobehavioral Reviews 24, 581–604.

Enard, W., Khaitovich, P., Klose, J., Zöllner, S., Heissig, F., Giavalisco, P., Nieselt-Struwe, K., Muchmore, E., Varki, A., Ravid, R., Doxiadis, G.M., Bontrop, R.E., Pääbo, S., 2002. Intra- and interspecific variation in primate gene expression patterns. Science 296, 340–343.

Fodor, J., 1983. The Modularity of Mind. MIT Press, Cambridge, MA.

Gelman, S.A., 2003. The Essential Child: Origins of Essentialism in Everyday Thought. Oxford University Press, New York, NY.

German, T.P., Barrett, H.C., 2005. Functional fixedness in a technologically sparse culture. Psychological Science 10, 1–5.

Hardy, K., Brand-Miller, J., Brown, K.D., Thomas, M.G., Copeland, L., 2015. The importance of dietary carbohydrate in human evolution. Quarterly Review of Biology 90, 251–268.

Hare, B., Call, J., Tomasello, M., 2001. Do chimpanzees know what conspecifics know? Animal Behaviour 61, 139–151.

Hare, B., Brown, M., Williamson, C., Tomasello, M., 2002. The domestication of social cognition in dogs. Science 298, 1634–1636.

Hull, D.L., 1986. On human nature. In: Proceedings of the Biennial Meeting of the Philosophy of Science Association. Volume Two: Symposia and Invited Papers, vol. 1986. Philosophy of Science Association, University of Chicago Press, Chicago, IL, pp. 3–13.

Ingold, T., 2006. Against human nature. In: Aerts, D., Gontier, N., Van Bendegem, J.P. (Eds.), Evolutionary Epistemology, Language and Culture. Springer, Dordrecht, pp. 259–281.

Johnson, K., Shiffrar, M. (Eds.), 2013. People Watching: Social, Perceptual, and Neurophysiological Studies of Body Perception. Oxford University Press, New York, NY.

Johnson-Frey, S.H., 2004. The neural bases of complex tool use in humans. Trends in Cognitive Sciences 8, 71–78.

Kaas, J.H., 2000. Why is brain size so important: design problems and solutions as neocortex gets bigger or smaller. Brain and Mind 1, 7–23.

Kaas, J.H., 2006. Evolution of the neocortex. Current Biology 16, R910–R914.

Kemler Nelson, D.G., Frankenfield, A., Morris, C., Blair, E., 2000. Young children's use of functional information to categorize artifacts: three factors that matter. Cognition 77, 133–168.

Krubitzer, L., Huffman, K.J., 2000. Arealization of the neocortex in mammals: genetic and epigenetic contributions to the phenotype. Brain, Behavior and Evolution 55, 322–335.

Laland, K.N., Odling-Smee, J., Feldman, M.W., 2001. Cultural niche construction and human evolution. Journal of Evolutionary Biology 14, 22–33.

Lyons, D.E., Young, A.G., Keil, F.C., 2007. The hidden structure of overimitation. Proceedings of the National Academy of Sciences of the United States of America 104, 19751–19756.

Mayr, E., 1963. Animal Species and Evolution. Harvard University Press, Cambridge, MA.

Meunier, D., Lambiotte, R., Fornito, A., Ersche, K.D., Bullmore, E.T., 2009. Hierarchical modularity in human brain functional networks. Frontiers in Neuroinformatics 3, 37.

Natterson-Horowitz, B., Bowers, K., 2012. Zoobiquity: What Animals Can Teach Us About Being Human. Knopf, New York, NY.

Penn, D.C., Holyoak, K.J., Povinelli, D.J., 2008. Darwin's mistake: explaining the discontinuity between human and nonhuman minds. Behavioral and Brain Sciences 31, 109–130.

Perry, G.H., Dominy, N.J., Claw, K.G., Lee, A.S., Fiegler, H., Redon, R., Werner, J., Villanea, F.A., Mountain, J.L., Misra, R., Carter, N.P., Lee, C., Stone, A.C., 2007. Diet and the evolution of human amylase gene copy number variation. Nature Genetics 39, 1256–1260.

Povinelli, D.J., 2000. Folk Physics for Apes: The Chimpanzee's Theory of How the World Works. Oxford University Press, New York, NY.

Preuss, T.M., 2000. What's human about the human brain? In: Gazzaniga, M. (Ed.), The New Cognitive Neurosciences, second ed. MIT Press, Cambridge, MA.

Preuss, T., 2004. What is it like to be a human? In: Gazzaniga, M.S. (Ed.), The Cognitive Neurosciences, third ed. MIT Press, Cambridge, MA, pp. 5–22.

Rakoczy, H., Schmidt, M.F., 2013. The early ontogeny of social norms. Child Development Perspectives 7, 17–21.

Richerson, P., Boyd, R., 2005. Not by Genes Alone: How Culture Transformed Human Evolution. University of Chicago Press, Chicago, IL.

Richerson, P., 2015. Human nature. In: Brockman, J. (Ed.), This Idea Must Die. Harper Collins, New York, pp. 88–91.

Rilling, J.K., Glasser, M.F., Preuss, T.M., Ma, X., Zhao, T., Hu, X., Behrens, T.E., 2008. The evolution of the arcuate fasciculus revealed with comparative DTI. Nature Neuroscience 11, 426–428.

Rizzolatti, G., Arbib, M.A., 1998. Language within our grasp. Trends in Neurosciences 21, 188–194.

Steffen, W., Crutzen, P.J., McNeill, J.R., 2007. The Anthropocene: are humans now overwhelming the great forces of nature? AMBIO: A Journal of the Human Environment 36, 614–621.

Striedter, G.F., Northcutt, R.G., 1991. Biological hierarchies and the concept of homology. Brain, Behavior and Evolution 38, 177–189.

Striedter, G.F., 2005. Principles of Brain Evolution. Sinauer Associates, Sunderland, MA.

Tennie, C., Call, J., Tomasello, M., 2009. Ratcheting up the ratchet: on the evolution of cumulative culture. Philosophical Transactions of the Royal Society B: Biological Sciences 364, 2405–2415.

Tishkoff, S.A., Reed, F.A., Ranciaro, A., Voight, B.F., Babbitt, C.C., Silverman, J.S., Powell, K., Mortensen, H.M., Hirbo1, J.B., Osman, M., Ibrahim, M., Omar, S.A., Lema, G., Nyambo, T.B., Ghori, J., Bumpstead, S., Pritchard, J.K., Wray, G.A., Deloukas, P., 2007. Convergent adaptation of human lactase persistence in Africa and Europe. Nature Genetics 39, 31–40.

Wellman, H.M., Cross, D., Watson, J., 2001. Meta-analysis of theory-of-mind development: the truth about false belief. Child Development 72, 655–684.

Chapter 29

Human Diversity at the Individual and Population Levels, and Societal Hierarchies

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INTRODUCTION

Hierarchies are ubiquitous in human societies, but describing the multiple forms that they can take is a formidable challenge. Part of the problem is that we use the concept of hierarchies to refer to various types of relationships between people: the bully intimidating younger children in the schoolyard, the natural leader mobilizing his peers to take part in an exciting project, the director of a large corporation having formal authority over his employees, the traditional chief using his wealth to support a large network of loyal clients, the religious leader claiming authority to interpret scripture, the prosperous professional benefiting from higher standards of living than her working class peers, etc.

My objective in this chapter is not to provide an exhaustive description of the various forms that hierarchies can take in human societies. This would clearly be impossible, as potential variations are infinite. My goal is more modest. I aim to explain that hierarchies are the outcome of a limited set of mechanisms working at different levels: biological, psychological, and social. My key message is that, despite interesting parallels with animals and especially apes, humans create societal hierarchies that have no equivalent in the animal kingdom. The creation of human hierarchies is made possible by unique social-cognitive skills and is a precondition to extending cooperation beyond a few dozen people. The paradox, I will claim, is that while human hierarchies result from our exceptional capacity for cooperation, they also make possible unprecedented levels of violence and exploitation.

I begin the chapter by explaining in broad terms what dominance hierarchies in the animal kingdom consist of and present the main mechanisms that lead to their emergence (section: Hierarchies and Dominance in the Animal Kingdom). I then provide a brief overview of the research aimed at documenting the presence in humans of these mechanisms, including research on the link between social status and hormones, behavior, and health outcomes (section: Do Humans Have Hierarchies?). I will argue that the dynamics of hierarchy formation among humans differs strongly from other species because of our unique mind-reading capacity and prosocial motivations (section: Uniquely Human Social Cognition). During the evolution of the genus *Homo*, our ancestors gradually developed an unprecedented capacity to cooperate and resist would-be alpha males, which led to the creation of relatively egalitarian social organizations among small foraging bands (section: How Our Ancestors Challenged Hierarchies). The last two sections of the chapter examine the current paradox with human hierarchies in more detail. On the one hand, we need large hierarchical organizations to support cooperation between thousands, if not millions, of people (section: Why Hierarchies Are Functional). On the other hand, well-studied social and psychological mechanisms open up the possibility that rulers will turn into despots and use hierarchies for exploitation (section: From Cooperative to Exploitative Hierarchies).

HIERARCHIES AND DOMINANCE IN THE ANIMAL KINGDOM

Farmers and herders must have been aware for centuries, if not millennia, of the existence of relationships of dominance among animals, that is to say, of the presence of

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00029-6

individuals who were more assertive, aggressive, and tended to harass and impose themselves over others. It is not until the 20th century, however, that dominance hierarchies were brought to scientific attention, after Norwegian zoologist Thorleif Schjelderup-Ebbe published his dissertation on the question. Schjelderup-Ebbe (1922) crafted the concept of "pecking order" (*Hackordnung*) to describe the strict sequence in which chickens were allowed to access food. Since then, dominance hierarchies have become a standard object of study among biologists and have been largely documented in countless species, ranging from crustaceans and fishes to birds and mammals. A large literature has documented the factors influencing the formation and maintenance of hierarchies in different species.

A first group of variations concerns the stability of hierarchies: while ranking is fixed for long periods of time in some species (or in some contexts), it remains fluid in others. Hierarchies are sometimes linear and transitive (such that if A dominates B, and B dominates C, A dominates C), but sometimes not. Hierarchies are partly determined by individual attributes, so that larger, healthier, more aggressive and more assertive individuals tend to dominate smaller, weaker, and more diffident ones. But hierarchies also vary in function of contextual factors, such as predation pressure, environmental stress, or feeding and sexual competition. The social intelligence of a species also determines how it forms and maintains hierarchies, as cognitively more sophisticated species, such as primates can form coalitions that play a crucial role when disputing rank. Among chimpanzees, for instance, raw physical force is instrumental in rising through the ranks, but social intelligence and the capacity to forge alliances and enlist supporters are also crucial for ambitious individuals to find their way to the top (de Waal, 1982).

Significant work has been done not only to characterize dominance hierarchies, but also to explain their existence. At the higher level of explanation, one can say that hierarchies result from the very nature of social life, in which animals are simultaneously in competitive and cooperative relationships with one another. On the one hand, living in groups can be a major source of well-being for animals. Conspecifics sometimes help protect against predators, access certain sources of food (eg, larger prey), and invest in offspring. At the same time, social life is a source of rivalry, especially when it comes to feeding and reproduction. Dominance hierarchies exist because animals are at an advantage if they can avoid permanent fighting, while drawing benefits from life in society. Once in place, stable hierarchies can be to the advantage of everyone. Dominants do not need to engage in permanent combat with subordinates to maintain their privileges, while subordinates can avoid taking the risk of challenging higher-ranking individuals in vain.

A more fundamental question is why animals strive toward higher social ranks in the first place. The generally accepted answer is that high-ranking individuals have greater access to feeding and mating opportunities, which leads to higher fitness (Clutton-Brock, 1988; Buss, 2007; Cummins, 2005). This view explains why the drive toward dominance is generally greater among males than among females. In most species, males and females do not face the same evolutionary trade-offs. For males, sperm is abundant and cheap, while reproduction is generally costlier to females (this is particularly true of mammals). For this reason, male reproductive success is much more variable than women's. As David Buss (2007, p. 360) puts it: "Nearly all fertile females will succeed in reproducing, regardless of their social status, but the same cannot be said of all fertile males. For each man who gains reproductive access to a disproportionate share of women, other men are consigned to bachelorhood and reproductive oblivion." In his survey of 700 studies, Ellis (1995) argues that high-ranking males typically have a reproductive advantage over low-ranking ones. The link, however, is not universal, revealing that subordinate males sometimes find ways to compensate for their disadvantage and highlighting the need to pay close attention to context when studying dominance hierarchies and their impacts.

Significant research has also been conducted to uncover the neurocognitive and behavioral mechanisms involved in the creation of dominance hierarchies. These mechanisms present interesting variations and similarities across species. Sheri Johnson et al. (2012, p. 692) have used the concept of dominance behavioral system (DBS) to refer to the "series of biological, psychological, and behavioral components" that "serve the organism's goal of control over social and material resources that are critical for survival and reproduction." The DBS is composed of a mechanism that monitors the environment to detect threat to one's rank, as well as a motivational system that direct action toward the goal of controlling resources. The drive to rise through the ranks is not the same for different individuals and can also vary depending on the social-cognitive abilities of each species. At the behavioral level, the DBS generally takes the form of easily recognizable gestures and displays of dominance and subordination. Among chimpanzees, for instance, dominant individuals make assertive and aggressive movements and try to appear larger and heavier, while subordinates lower their bodies, present their rear-ends or emit pant-grunts as they look up at higher-ranking individuals (de Waal, 1982). Failing to display signs of submission comes with the risk of being punished.

At the biological level, there is a close connection between dominance behavior and the neuroendocrine system that regulates the production of hormones, such as testosterone and cortisol (Sapolsky, 2004a,b; 2005). For instance,

there is an unambiguous link between aggression, the drive toward dominance, and the production of testosterone. It has long been known, for instance, that castrated rodents barely ever fight, but resume combat when testosterone is administrated to them (Beeman, 1947). Among birds, Wingfield et al. (1990) proposed the so-called "challenge hypothesis" to account for changes in patterns of testosterone production and aggression in the context of seasonal breeding. According to this hypothesis, testosterone increases among males at the onset of the breeding season and reaches its peak to support male−male aggression in the context of territory formation and mate guarding. The challenge hypothesis has been particularly effective at explaining patterns of testosterone changes among birds, but has also been applied to a large array of species, including fishes (Wingfield et al., 2000; Hirschenhauser et al., 2004).

The relationship between aggression and testosterone production has also been closely studied among primates. High-ranking chimpanzees, for instance, constantly harass and randomly aggress low-ranking ones and, as expected, rank is a good predictor of testosterone secretion (Muller and Wrangham, 2004; Muehlenbein et al., 2004). Gesquiere et al. (2011) established that, among savannah baboons (*Papio cynocephalus*), high-ranking males also have higher testosterone levels. But the link between testosterone and rank is not always straightforward. In closely related chacma baboons (*Papio hamadryas ursinus*) from Okavango Delta, for instance, rank is not related to testosterone levels after controlling for age. A close connection is rather to be found between testosterone and *changes* in rank (Beehner et al., 2006). Individuals with high testosterone are more aggressive and more likely to rise in the hierarchy, while those with low testosterone are more likely to go down.

A key point to keep in mind is that testosterone is costly to produce at the metabolic level and triggers immunosuppression. As a result, secreting high levels of testosterone continuously comes with significant costs in terms of fitness. It is no surprise thus that the connection between testosterone and rank depends on the level of aggression required to maintain one's position. When hierarchies are stable and high-ranking males remain unchallenged for a certain time, secreting too much testosterone is of little use. This is the case with chacma baboons (Beehner et al., 2006). But in fission−fusion chimpanzee communities, challenges are unpredictable and secreting more testosterone on a permanent basis can pay off.

Primatologists have also studied the link between dominance hierarchies and another group of hormones. Among mammals, glucocorticoids (especially cortisol) are closely related to stress responses. More precisely, in the presence of a stressor (eg, a predator), the adrenal gland produces cortisol, which, in turn, stimulates the production of glucose, increases blood pressure and muscle tension, and gives the body the boost of energy it needs for a quick response: fight or flight. As with testosterone, the secretion of cortisol comes with costs, in that it is also linked to immunosuppression, leading to higher risk of illness. As neuroendocrinologist Robert M. Sapolsky (2004b) famously argued, the stress response makes perfect sense from an evolutionary viewpoint. In the face of an imminent threat (eg, a lion), the right thing for the zebra to do is to mobilize all possible energy and to run as fast as it can. Turning off immunosuppression for a brief period of time is not a major issue. However, among social animals, including humans, some stressors are not as temporary as a lion attack. This is the case with the persistent stress that can result from dominance relationships. So-called "chronic stress" leads to the prolonged secretion of glucocorticoids and increases the risk of a broad variety of diseases, including ulcers, sterility, stunted growth, hypertension, arteriosclerosis, cardiovascular disease, type 2 diabetes, and osteoporosis (Sapolsky, 2004a,b; McEwen and Lasley, 2002).

For decades, Sapolsky et al. have studied the social behavior of a troop of wild baboons in Kenya. As with many primate species, life at the bottom of the hierarchy can be nasty, with low-ranking individuals having to endure random attacks and daily persecution from high-ranking ones. Being constantly pushed around when one tries to eat or rest is a form of terror that can lead to chronic stress. Elizabeth Archie et al. (2012) have shown that, among wild baboons from Kenya, rank is a good predictor of how well an individual will recover from a wound, which seems to be at least partially linked to the immunosuppressive impact of glucocorticoid secretion and chronic stress.

As for testosterone, the link between chronic stress, glucocorticoids, and rank is not straightforward. In a stable dominance system, individuals at the bottom of the hierarchy tend to be subject to most of the physical and psychological stressors, but things are different when hierarchies are unstable (Sapolsky, 1993). In periods of uncertainty, alpha males and other high-ranking individuals have to constantly remain on their guard. They experience significant stress as their position is openly challenged. Studying a group of mandrills, for instance, Setchell et al. (2010) found that glucocorticoid levels were higher among subordinates in times of stability, but higher among high-ranking males in times of social unrest. Because of the link between chronic stress and immunosuppression, high-ranking males showed a greater variety of gastrointestinal parasite infections. Similarly, in some baboon troops, being in the top position is associated with persistent stress, and glucocorticoids are significantly higher among alpha males than among second-ranking males (Gesquiere et al., 2011).

If ranking high can be a source of stress in many contexts, ranking low does not necessarily mean that one's life

will be miserable. A metaanalysis of research conducted among seven primate species has shown that stress among low-ranking primates is a function of two variables: (1) the rate of stressors to which individuals are exposed, for instance, in the form of harassment by dominants, and (2) the opportunities they have to find social support, especially among kin (Abbott et al., 2003). As a result, ranking low can turn out to be a blessing under some circumstances, for instance, in old age. As Sapolsky (2004b, p. 393) comments in the case of wild baboons, males that have always ranked low in the hierarchy often age surrounded by familiar kin and friends, among whom they can find relief in times of stress. On the other hand, former alpha males can be traumatized by the experience of losing rank and, under harassment from younger individuals, can be forced to move into another troop, where they will end their days miserably in the company of strangers.

Dominance hierarchies are not only the outcome of individual attributes and various contextual factors. As the social dynamics unfold, they shape the minds and brains of individuals in a way that determines their further capacity to thrive. In a study of squirrel monkeys, Kirk R. Manogue et al. (1975) have shown that social rank shapes individual responses to stressors. Alpha males had low baseline cortisol levels, which suggests that they had not been exposed to prolonged stress. When exposed to a stressor, however, they had a large increase in cortisol, the kind of response that prepared them well for an energetic reaction. Subordinates, by contrast, had a higher baseline and significantly lower increase in response to a stressor. This pattern suggests that chronic exposure to stress had left subordinates with blunted responses in the face of new challenges, a situation that left them ill-positioned to react to stressful events.

Dominance relationships do not only shape the brain of cognitively complex species like primates. When two male crayfish meet, for instance, they engage in a fight to establish dominance. The loser moves away and avoids further contact with the winner. Such fights have been shown to shape the responses of a specific neuron in the crayfish's brain (Yeh et al., 1996). Among winners, the neuron is more likely to be activated in the presence of the neurotransmitter serotonin, which is associated with aggressive behavior in this species. Among subordinates, by contrast, activation of this neuron is more likely to be inhibited. This neural change is not without consequence: when two subordinate crayfish are put in competition, they engage in a fight and one ends up dominating the other. But things work out differently when previously dominant males are placed in competition: a fight is engaged, but the losing crayfish seems unable to accept his subordination, and keeps engaging the dominant one at the risk of being killed. Because of similar neural changes, social dynamics can significantly shape dominance hierarchies. Initial wins and losses in the competition for status help determine how individuals will behave in further combats. This feedback loop has been claimed to explain why initial attributes, such as size and aggressive behavior are insufficient to predict the outcome of hierarchy formation among fishes (Chase et al., 2002).

DO HUMANS HAVE HIERARCHIES?

Dominance hierarchies among animals are the outcome of a large complex of variables: individual attributes rooted in biological mechanisms, social and environmental factors, as well as the feedback between them. What about properly human hierarchies? I will argue that, because of our unique social-cognitive skills, we form hierarchies that are profoundly different from the ones formed by other primates. But significant research has also documented the importance of the various mechanisms among humans described earlier in this chapter. This section briefly summarizes this research before explaining how humans differ from other species in the rest of the chapter.

A first similarity between humans and other animals is found in the presence of individual variations as to how people behave in competitive social settings. The presence of a drive for dominance is clearly present in humans and has been documented through various psychological constructs. Individuals with so-called "type-A personalities," for instance, have been described as prone to being impatient, hostile, aggressive, and competitive (Friedman, 1996). In his book on the psychology of social class, Michael Argyle (1994, pp. 54–55) contrasts the behavior of dominant individuals who stand with straight posture and an expanded chest, and who look at others and gesture, with the bent posture of submissive individuals who give deferential head nods, speak less, and do not interrupt high-status persons.

Several authors have also described important gender differences with respect to dominance. Moskowitz (1993), for instance, has shown that, in a cooperative setting, men tend to be more dominant than women, especially when interacting with other men. In his study, dominance is defined as the disposition to try to influence others or the outcome of a situation, with key behaviors including telling the other person what to do, taking control of the resources necessary to solve the problem, and ignoring the other person. Reviewing the large literature on the question, Eleanor Maccoby (1990) has argued that significant gender differences with respect to dominance and competition already exist in preschool years. Boys tend to prefer a rough-and-tumble play style and use language in an egoistic fashion. Girls, by contrast, tend to use conversation as a binding process and find it difficult to influence boys.

A large literature has also examined how informal hierarchies rapidly emerge through group dynamics. Fisek

and Ofshe (1970) have observed how the distribution of speaking time and the capacity to influence group decisions evolved in groups of three people meeting for the first time. They found that a clear differentiation appears within a few minutes of the beginning of the conversation, with some individuals taking more place and having more influence on outcomes than others. In a similar spirit, Kalma (1991) has shown that individuals are good at predicting how much place they will have in a discussion as soon as they have seen other participants, but before a word has been spoken. This and similar studies have been taken as evidence that dominance hierarchies do not only exist, but play a pervasive role in small groups and face-to-face interactions (Booth et al., 2006).

Another influential stream of research has examined the hormonal correlates of aggression, competition, and dominance. As with other primates, testosterone plays a crucial role. A study conducted among inmates revealed that men with high testosterone levels were more likely to have committed crimes involving physical violence than property crimes, such as burglary and theft, and they were also more likely to have overtly transgressed prison rules (Dabbs et al., 1995). Testosterone levels are also predictive of criminal violence and aggressive dominance among women (Dabbs and Hargrove, 1997). A large number of studies have also examined changes in testosterone in competitive settings, especially in sports (for review, see Booth et al., 2006). The best-established result is that testosterone increases in the face of a challenge, as one anticipates the efforts to come. After the competition, testosterone remains high among winners but declines among losers. This pattern can also be observed among voters who win or lose an election (Stanton et al., 2009). Similar results have been used to argue that there is a reciprocal relationship between hormonal secretion and social dynamics in humans as in many other species (Mazur and Booth, 1998). Testosterone levels influence how one performs in competitive social settings, but the reverse is also true. The outcome of social interactions determines further testosterone levels.

That being said, the relationship between testosterone and dominance is far from straightforward. Studies of college students, for instance, have established that young men and women with higher testosterone levels have a more engaging and confident interaction style, which could be conducive to more helpful behavior (Dabbs et al., 2001). These findings suggest that the link between dominance and testosterone, although present in humans, is strongly modulated by our disposition to cooperate and capacity to inhibit aggression (Christiansen, 1998). It also helps explain why the relationship between testosterone and social status among humans is more intricate than among other primates. Those of us with high levels of testosterone are far from being guaranteed a high rank in society. In fact, there is a negative association between testosterone levels and social status in men, at least when status is defined in terms of occupational prestige and income (Dabbs, 1992). This negative association is of limited amplitude, however, and high testosterone men can also find their way to prestigious positions in society. Mazur and Booth (1998) have argued that high testosterone can motivate both prosocial and antisocial behaviors, pushing some individuals toward the bottom of the occupational hierarchy, and others toward the top.

A large stream of research has looked into the physical, behavioral, and health correlates of socioeconomic status (SES). A well-researched relationship exists, for instance, between height and SES. Various explanations have been proposed to account for this link, including self-esteem and dominance, but also the presence of an advantage in cognitive skills among taller persons (Case and Paxson, 2008). In a similar spirit, Schmitt and Atzwanger (1995) measured the speed at which people walk through Vienna. They then stopped the people to inquire about their SES. They noted that men of higher SES walked significantly faster than men of lower status (although they found no such correlation among women). Height and walking speed are not the only variables predictive of SES. Mueller and Mazur (1996) have examined the link between military rank and facial dominance, indicated by a prominent chin, heavy brow ridges, and a muscular face. Using photographs from the military academy, they rated the facial dominance of 434 West Point cadets and then found that it was correlated with military ranks attained more than 20 years later. Cadets with low facial dominance—indicated by a weak chin, slight brow ridges, and a fleshy face—were less likely to have gone up in the hierarchy.

The relationship between SES and health has also attracted significant attention. The famous Whitehall study, for instance, examined the health correlates of rank among members of the British civil service over several decades (Marmot et al., 1991). The study found a strong relationship between rank and the prevalence of illness, high blood pressure, obesity, smoking, and associated mortality risks. This relationship is also supported by a large literature in public health, revealing the existence of a consistent gradient where individuals of low SES face greater health risks, independent of factors, such as access to health care or the dangers inherent in one's occupation (Rivers and Joseph, 2010). The relationship between health and status is even stronger when subjective SES (one's perceived status) is taken into account rather than objective SES. A study by Adler et al. (2000) found that subjective SES in women is associated with heart rate, sleep latency, abdominal body fat, and hyperactive cortisol response to chronic stress, even after controlling for objective SES. Individuals with higher perceived status are also less at risk of developing the common cold (Cohen et al., 2008). The relationship

between subjective SES and health is arguably mediated by the stress resulting from perceiving oneself as in a position of subordination relative to other people.

One key question is whether the human drive to attain higher status, especially among men, is driven by the same evolutionary logic present in most other species. In other words, is the ultimate cause of the quest for high status the outcome of dominant individuals' greater fitness? Several authors have argued in favor of this hypothesis (Cummins, 2005; Buss, 2007). Evolutionary psychologist Laura Betzig (1993), for instance, examined the link between rank and reproductive success among six early civilizations (Mesopotamia, Egypt, India, China, Incan Peru, Mexico). She found that in all cases, rulers maintained large harems composed of dozens and sometimes hundreds of fertile women. In some cases, the reproductive success of the despots has been so large that it can still be traced in contemporary populations. The most famous case is that of the Mongol ruler Ghenghis Khan. A study of the population from the territory covered by the former Mongolian empire suggests that no less than 8% of the men from this region descend from the famous emperor and his sons (Zerjal et al., 2003). The link between social status and reproductive success remains controversial, however, because of the way social norms (eg, monogamy) and technologies (eg, contraception) influence sexuality and reproduction. Nevertheless, studies of both premodern and modern societies have tended to find a positive link between social status, wealth, and fertility among men (but not among women), suggesting that status pays off in evolutionary terms in a broad variety of social contexts (Fieder et al., 2011).

UNIQUELY HUMAN SOCIAL COGNITION

Research reviewed in the previous sections has shown interesting parallels between human and nonhuman hierarchies. This research, however, raises important definitional issues. Human hierarchies are sometimes defined in a way that is similar to those in animal studies. A relationship of dominance is said to exist, for instance, when one individual is assertive and aggressive and the other diffident and deferent. But the concept of a dominance hierarchy is often extended to refer to any type of inequality, including the existence of social classes, occupational and wealth inequalities, and institutional authority. This extension is problematic, given the complexity of human societies. As Sapolsky (2004b, p. 363) puts it:

> *So, the lowly subordinate in the mailroom of the big corporation may, after hours, be deriving tremendous prestige and self-esteem from being the deacon of his church, or the captain of her weekend softball team, or may be at the top of the class at the adult-extension school. One person's highly empowering dominance hierarchy may be a mere 9-to-5 irrelevancy to the person in the next cubicle, and this will greatly skew results.*

What is often missing in discussions of human hierarchies is a cogent account of how human culture and unique social skills alter the dynamics of hierarchy formation. This is what this section and the following aim at providing. The concept of culture is arguably the most important in the study of human societies and, at the same time, the hardest to define (Kroeber and Klockhohn, 1952). Explaining what we mean by culture is made even harder by the growing recognition that several species across the animal kingdom—including apes, but also cetaceans and birds—adopt socially transmitted behaviors (Laland and Galef, 2009). Fortunately, a rapidly expanding literature, comparing human and nonhuman psychology, helps in discerning what is so specific about human social cognition.

Summarizing human specificity in one sentence, we might say that we are wired to be attuned to one another. This attunement begins from the earliest age and shapes the way we interact with one another throughout our lives. Indeed, from their first days of life, newborns are sensitive to others' emotional states. A baby that hears the cries of another child is more likely to start crying, just as one that sees a smile is more likely to smile, a phenomenon known as emotional contagion (Martin and Clark, 1982). Such reactions appear so early in child development that they are unlikely to be the result of social learning. In all likelihood, they are based on hardwired mechanisms that match our affective reactions of pleasure and displeasure to those of our peers.

Newborns' attunement to others is obviously limited by the narrowness of their understanding of the world. But it offers the basis on which they build more complex cognitive skills. From 9 to 12 months, for instance, children begin to actively monitor the gaze of their parents and take an increasing pleasure in sharing their attention. The ingenuous interest that a toddler finds in pointing objects out to his parents may not be impressive at first sight, but it has no equivalent in the world of primates (Tomasello, 2010, 2014). Apes, for instance, can learn hundreds of symbols from sign language, as the famous examples of the bonobo Kanzi and the gorilla Koko have shown. But they approach language in a way that is very different from toddlers. Instead of taking pleasure in the simple act of referring to things, they use language in an almost exclusively instrumental manner.

It would be hard to overemphasize how the pleasure we take in sharing each other's attention and emotions transforms our life and societies. It is not only at the foundation of properly human language; it is also the ground on which altruism, cooperation, social norms, and morality can

develop. Take altruism, for instance. Carolyn Zahn-Waxler et al. (1992) have studied how concern for others develops in toddlers. Between the ages of one and three, children respond increasingly clearly to the presence of a person in distress. For instance, they will approach a person that simulates pain and try to comfort her with a hug, by handing her a doll, by inquiring if everything is okay or by manifesting sadness. Felix Warneken et al. (2006) have shown that 18-month-old toddlers spontaneously try to help an adult retrieve a marker that the adult accidentally dropped on the floor or to open the door of a cabinet that the adult is manifestly unable to open. They found that similar helping behaviors are present among chimpanzees, although significantly less robust, arguably because of apes' limited abilities to infer more complex goals (or a limited interest in doing so).

It is true that apes' social cognition is significantly more complex than once believed. There is a growing consensus, for instance, that apes are capable of representing others' intentions. Placed in competition with an alpha male for a favored food, a subordinate chimpanzee first finds out if the dominant individual can see the food and then decides whether it is safe to approach it or not (Hare et al., 2000). Similarly, chimpanzees can differentiate, on the basis of subtle behavioral cues, between an experimenter who refuses to give them food intentionally and another who fails to deliver it accidentally (Call et al., 2004).

Children's understanding of the social world, however, grows rapidly beyond that of their primate cousins. They also begin by inferring simple goals in their first year of life, but they progressively develop more complex models of how others see the world. This is most obvious in their understanding of false beliefs. In a classical experiment, a puppet named Sally takes a marble, puts it in a basket and then leaves the room. A second puppet, Anne, then takes the marble out of the basket and puts it in her own box. When Sally comes back into the room, the experimenter asks children: where will Sally look for her marble? Will she look in the basket (where she thinks it is) or in the box (where the children know it is)? Research in psychology demonstrates that, before 4–5 years of age, children claim that Sally will look in the box, failing to take into account her false belief (Wimmer and Perner, 1983; Baron-Cohen et al., 1985). After this age, however, they grasp that she will look in the basket, because she has no reason to think that Anne moved the marble into the box. This is not case, however, for autistic children, who tend to fail the test even when they grow older.

Extensive research over the past decades has refined our understanding of false beliefs. First, it is now widely accepted that children younger than 4 or 5 years of age do have some grasp of false beliefs, although only at the implicit level. Indeed, toddlers between the ages of one and two are surprised if Sally looks for the marble in the box, when she should not know that it has been displaced (Onishi and Baillargeon, 2005; Surian et al., 2007). In other words, children do have a cognitive model of false beliefs, but they are still unable to verbalize it. Second, research has established with a high degree of confidence that apes do not understand false beliefs in settings similar to the Sally and Anne test (for review, see Tomasello and Moll, 2013). Third, the understanding of false beliefs is associated with the broader capacity of young children to articulate multiple perspectives on objects, for instance, the capacity to imagine how an object looks from different points of view or to understand that appearance can differ from reality (Flavell et al., 1983; Perner et al., 2002).

Human-specific social motivations and skills allow for the emergence of social norms and more complex institutions. As early as age three, for instance, young children understand that games have rules, and insist that these rules be respected (Schmidt and Tomasello, 2012). Rakoczy et al. (2008), for instance, taught three-year-old children a simple game called "Dax." At some point, a puppet called "Max" arrives and says he also wants to play Dax. If the puppet failed to play correctly, children intervened to stop him: "No, this is not how you play!" By contrast, if Max did not say that he wanted to play Dax, but rather that he wanted to show something interesting to the children, they did not protest. The Dax game is obviously simpler than the most complex institutions that humans have created throughout history. Nevertheless, it illustrates the foundation on which human culture is built. We do not simply develop expectations toward one another (what other primates do). We also devise abstract games in which expectations are defined in function of one's role (Searle, 1995; Tomasello, 2014). A long learning process is needed for children to fully appreciate, for instance, how rights and obligations are allocated within complex institutions and how such institutions evolve over time.

Another important feature of human-specific social cognition is morality. There is significant controversy in psychology and philosophy concerning the exact functioning of moral judgment. Not everyone agrees on the way in which emotions, intuitions, reasons, and abstract considerations of fairness intervene in the distinction between good and evil (see, for instance, Prinz, 2007; Baumard, 2016; Mikhail, 2010; Haidt, 2012; Greene, 2013). There is broad agreement, however, that morality is somehow based on the sociocognitive and socioaffective skills that I just described, that is, on our capacity to read other minds and motivations to help and cooperate with others.

There is also no doubt that morality, through its connections with affects, motivates behavior in important ways. Indeed, moral judgment is linked to both positive and negative emotions, directed both toward oneself and others (Haidt, 2003). Good deeds, for instance, inspire pride in those who commit them, and admiration in observers.

Moral violations, by contrast, tend to elicit negative emotions, including guilt and shame in transgressors and indignation and anger in victims or third parties who witness the transgression. Here again, there is significant debate as to how exactly moral emotions motivate behavior (Fessler and Haley, 2003; van Winden, 2007; Clavien and Klein, 2010; Batson, 2011). There is no doubt, however, that under a broad range of circumstances, positive and negative emotions steer us away from moral transgressions. A large literature in experimental economics, for instance, has examined how emotions, such as anger and indignation can, under many circumstances, motivate the punishment of unfair behavior and promote cooperation (Gintis et al., 2006; Dubreuil, 2015).

Human-specific disposition to altruism, cooperation, norm following, and morality do not offset the mechanisms, discussed in the previous sections, that explain the formation of dominance hierarchies in the animal kingdom. They explain, however, why the process of hierarchy formation is much more complex among humans. Developmental psychology can shed a unique light on how the progressive integration of young children into the world of norms and morality influences dominance behavior. It is well established, for instance, that during preschool years, important changes happen as to how children try to influence others and take control of resources (Hawley, 1999; Pellegrini et al., 2007). While younger children tend to coerce others into doing what they want, older preschoolers switch to more subtle approaches based on cooperation, negotiation, and alliance formation.

This is not to say that coercion, aggression, and intimidation play no role among older children. As adults, they remain capable of gross forms of violence and abuse. Nevertheless, the socialization process, the development of social norms and moral judgment, changes what can and cannot be an effective way of influencing others dramatically. In the social world of humans, the drive to dominance can rapidly lead to appalling consequences if one is incapable of controlling one's impulses and regulating one's emotions. In fact, we care so much about how people regulate the drive to dominance that we recognize various conditions that prevent people from regulating their emotions as mental disorders. This is the case for antisocial disorders and psychopathy and also for disorders, such as narcissism and mania, related to an inflated view of one's power and value (Johnson et al., 2012).

HOW OUR ANCESTORS CHALLENGED HIERARCHIES

Most humans today live in societies where hierarchies and inequalities are ubiquitous: large corporations, religious organizations, and governments are all organized hierarchically, and there is a dramatically unequal distribution of wealth, health, and well-being. This makes it easy to lose sight of the fact that, from the perspective of our evolutionary history, this situation is totally extraordinary. For hundreds of thousands of years, our ancestors lived in small foraging bands with limited inequalities and no wealth as we know it. How did our ancestors evolve, from ape-like dominance hierarchies to a properly human way of life? Reconstructing our evolutionary past cannot be done through direct observation. It must rely on an inference to the best explanation, drawing from research from a variety of disciplines, including paleoanthropology, archeology, anthropology, theoretical biology, and comparative cognitive neurosciences.

Ethnographies of historical foragers offer a good starting point for an inquiry into our evolutionary past, although it is true that the Inuit, Australian Aborigines, or San and Mbuti people are not relics of the distant Paleolithic. Indeed, most foraging people, even at the time of their first contact with European explorers, had already had significant contact with nonforaging people and, in some cases, had themselves been involved in agriculture in the past. Furthermore, questions can be raised as to whether modern foragers live in habitats that are representative of the ones found in the Paleolithic (Porter and Marlowe, 2007). Holding these caveats in mind, however, a comparative analysis of foraging societies can undeniably reveal how *Homo sapiens* tends to organize its social life in the absence of a state and wealth. One of the most common traits of foraging societies, for instance, and one that drew the attention of the first European explorers and ethnographers, was the absence of coercive political authority (Clastres, 1989). Indeed, throughout the world, foragers spend most of their time in small mobile bands comprised of a few dozen individuals, who are generally related to one another (Kelly, 1995; Lee and Daly, 1999). These bands are embedded in a broader social landscape and participate in fission-fusion networks: groups split and new groups are formed periodically as a function of marriage, affinity, and necessity.

Life in small bands and the fission-fusion dynamic are not proper to *Homo sapiens* but can be found in several primate species. What is interesting about human foragers, though, is the lack of a clear hierarchy, in which more robust and aggressive individuals impose themselves over others through bullying and harassment. Foraging societies are not strictly egalitarian. A division of labor exists along gender lines, as well as a marked power differential between younger and older individuals. Nevertheless, among adults, no one is in position to dominate others through the use of naked force. Moral suasion exists and individuals can demonstrate leadership, but there is no ruler capable of imposing his will to the group. Henrich and Gil-White (2001) described this form of leadership as "freely conferred deference" and contrasted it with dominance based on fear and threat.

The relative egalitarianism of foraging societies is facilitated by the very nature of their mode of subsistence. In the vast rainforest, desert, or tundra, most adults or households have the capacity to leave one group and join another one. In some cases, they can even subsist on their own. But the possibility of escaping potential bullies is not the main reason for the infrequency of open forms of dominance. The key to more egalitarian social relations among foragers is the disposition to cooperate, enforce social norms, and develop a sense of fairness. Anthropologist Christopher Boehm (2012) completed ambitious surveys of the ethnographic literature on foraging societies in order to find out how they counteracted the drive to dominance of more aggressive individuals. Among other things, he looked for instances in which capital punishment had been imposed on an individual. Not only did he find several instances of executions, but found that, in about half of the cases, the person put to death was a man who was intimidating the group through malicious sorcery or different forms of aggression (Boehm, 2012, pp. 83–85). In the other cases, the execution targeted individuals who had committed serious moral breaches (eg, violation of a taboo, sexual transgression, betrayal of the group).

Capital punishment is obviously a rare and extreme form of punishment. Imposing it is dangerous. There is a risk of retaliation, unless the entire group is in agreement with the sanction. Moreover, by carrying out an execution, a foraging band loses one of its members, someone who could contribute to the group's subsistence. As a result, social control takes significantly milder forms most of the time. Gossip, ridicule, and ostracism, for instance, are favored tools used against arrogant individuals who try to impose themselves over others, refuse to share, or adopt all kinds of antisocial behaviors. Such tools are efficient not only because foragers want to avoid the negative feeling of shame, but also because they care about social status. In a world in which cooperation is often needed for survival, maintaining a good reputation is crucial for finding partners and allies. In this sense, Baumard (2010) has argued that open and direct punishment is rather unusual among foragers, and that the motivation to behave fairly is, more often than not, driven by the need to position oneself as a partner of choice in the market of cooperation.

Boehm (1993, 1999) argues that the human capacity for social control and cooperation has led through evolution to the emergence of "reverse dominance hierarchies." In contrast to what happens in ape societies, aggressive and intimidating foragers generally fail to establish dominance over others and are instead pushed toward the bottom of the hierarchy, reversing the usual pyramid. There is little doubt that such a reversal occurred at some point in the human lineage. An interesting question, however, is when did it happened and what prompted it? Unfortunately, we do not have direct access to the social life of our forebears. We cannot directly observe how australopithecines, *Homo erectus* or Neandertals treated more aggressive individuals who tried to dominate others. Nevertheless, the archeological and paleoanthropological records can help document major transitions in social organization and modes of subsistence. A reasonable assumption is that we can read the gradual emergence of the disposition for cooperation in the human lineage in these transitions. As cooperation is what stands behind the capacity of foragers to oppose more aggressive and dominant individuals, finding the roots of cooperation is tantamount to finding the origins of equality among foragers.

In previous works (Dubreuil, 2010a,b; Henshilwood and Dubreuil, 2011; Dubreuil and Henshilwood, 2013), I argued that three major transitions can be identified in the human lineage, each of them coinciding with a significant change in social cognition and an increase in our forebears' capacity to cooperate. The first transition came with the slow emergence of the genus *Homo*, between 2.5 and 1.5 million years ago. This transition is linked with major changes in hominid morphology, including increased brain size in *Homo habilis*, *Homo ergaster*, and early *H. erectus*, the progressive loss of upper limb morphology facilitating climbing, and the evolution of morphological features adapted to long-distance walking and running (McHenry and Coffing, 2000). In all likelihood, this new morphology was linked to early humans moving into a new ecological niche. Early members of the genus *Homo*, in contrast with australopithecines, could not easily climb trees to find protection, but could walk long distances through more open landscapes in search of plants, small prey, or fresh carcasses to butcher, thanks to an increasingly regular use of stone tools (Ungar et al., 2006). I have argued that this new mode of foraging implied a greater capacity for cooperation, the kind that could be supported by a growing motivation to share attention and collaborate on joint tasks (Dubreuil, 2010a). Indeed, early humans could stay on the ground while protecting themselves against powerful predators (eg, lions, hyenas), they could support less mobile members of the group (eg, pregnant women, small children, wounded individuals) through long-distance walking, and could confront other scavengers to access carcasses early on.

The colonization of this new niche by early members of the genus *Homo* triggered an evolutionary process that spanned several hundreds of thousands of years. During the period between 1.5 and 0.3 million ybp, human brains grew slowly but steadily, suggesting a sustained evolutionary pressure for more advanced cognitive skills (Rightmire, 2004). Technology also progressed slowly, but major changes were introduced in the organization of social life. By the end of this period, our ancestors had mastered control over fire, which provided protection against predators and cold, but also facilitated digestion, leading to

important improvements in human diet. *Homo heidelbergensis* and Neandertals were no longer limited to small-game hunting and scavenging, but became top-level predators who could switch to large-game hunting when appropriate (Thieme, 1997; Richards et al., 2000). Large-game hunting provides strong evidence of advanced cooperation among early humans, not only because it has to be conducted in groups to be efficient, but also because there is no point in adopting such a risky mode of subsistence if hunters cannot find ways of sharing meat with one another and of bringing back carcasses to a base camp to feed small children, pregnant women, and incapacitated individuals, as modern *H. sapiens* do (Gurven, 2004).

Additional evidence of improving cooperation during this period is found in the changing life-history patterns of hominins (Kaplan et al., 2000). Indeed, one of the most striking characteristics of modern humans is the time they need to become adults. While chimpanzees can feed autonomously at about four years of age, human children typically cannot before adolescence. This prolonged period of dependence plays a crucial role for human children: they use it to develop their big brains. In fact, social, emotional, linguistic, and technical skills keep developing well into teenage years and young adulthood. But a longer childhood also has significant energetic implications: while female chimpanzees care for only one child at a time, women in foraging societies must typically care for two, three, or four. They can do it because, in contrast with female chimpanzees, they can count on the support of both female and male members of their band. Human cooperation and sharing is the key mechanism that explains the evolution of modern human life history, by supporting massive energetic transfers from adults to children.

Several studies have attempted to reconstruct the evolution of life history in the human lineage, by analyzing changes in morphology and, more precisely, patterns of dental and brain development (Robson and Wood, 2008). Although the evidence is generally hard to decipher, a prudent interpretation is that early *H. erectus* had already departed from the ape-like life history, indicating significant changes in the organization of its social life, but was also far from having developed the modern pattern. By contrast, more recent hominin species, such as *H. heidelbergensis* and Neandertal were closer to modern humans. Childhood and adolescence may not have followed exactly the same pattern, suggesting some differences at the cognitive and behavioral levels, but there is little doubt that raising children in these populations was a long and largely cooperative venture (Hublin et al., 2015).

A third key transition in the history of mankind is associated with the emergence of so-called "behavioral modernity," that is to say, of the set of behavioral traits typically associated with *H. sapiens*, including more complex and rapidly evolving technologies, as well as abstract representations and symbols. At least three major points of contention remain in the literature concerning the evolution of behavioral modernity. First, when exactly did behavioral modernity first emerge in the human lineage? For a long time, it was thought to coincide with the arrival of *H. sapiens* in Eurasia between 50,000 and 40,000 years ago. It is now broadly accepted that strong evidence of behavioral modernity—including abstract engravings, personal ornaments, and compound tools—were already in Africa in the period between 100,000 and 50,000 years ago, and arguably earlier (Henshilwood and Dubreuil, 2011). One possibility is that modern behavior progressively emerged with the evolution of morphologically modern *H. sapiens* around 200,000 years ago, but the evidence remains scarce and contested.

A second point of contention is the alleged presence of modern behavior among closely related Neandertals. Although the majority opinion among archeologists has long been that there was a significant cognitive and behavioral gap between Neandertals and *H. sapiens*, a number of findings raise questions about how the two groups differed from one another. One of them is the presumed existence of interbreeding between *H. sapiens* and Neandertals, as evidenced by the presence of Neandertalian genes in human population originating outside Africa (Green et al., 2010). Other findings concern material culture, including an abstract engraving found in a late Neandertal site in Gibraltar more than 39,000 years ago and the well-known existence of personal ornaments from the Grotte du Renne in France (Caron et al., 2011; Zilhão, 2012; Rodriguez-Vidal et al., 2014). Although substantial controversy remains concerning the modernity of Neandertals, a prudent conclusion is that they formed a highly cooperative population, with advanced social cognition, and that the behavioral gap between them and *H. sapiens* may not have been unbridgeable.

A third open question concerning modern behavior is how to account for its evolution at the neural and cognitive levels. Although most authors agree that its emergence had something to do with the evolution of social cognition (including language or culture), researchers do not necessarily agree on what particular changes in the human mind and brain led to the emergence of symbolism, art, and rapid technological progress. My own proposal (Dubreuil, 2010a; Henshilwood and Dubreuil, 2011; Dubreuil and Henshilwood, 2013) is that modern behavior resulted from advancements in mind reading and, more precisely, from the development of the capacity, described earlier (section: Uniquely Human Social Cognition), to represent the world through the eyes of others. The capacity to imagine how people see things (and not simply to understand, as apes do, that they see things) has allowed early *H. sapiens* to develop an interest in their own appearance and reputation, as well as in objective representations of situations and meanings.

Independent of the details of our evolutionary history, a few indisputable facts need to be emphasized. The main one is that humans, over the past 2 million years, moved into an evolutionary niche that fostered the adoption of new modes of subsistence based on unprecedented levels of cooperation. There is no question that this new social organization was accompanied by major cognitive and affective changes through the selection of unique prosocial motivations, mind-reading skills, and forms of communication.

Further debates concern the precise selection mechanism that led to the evolution of human-specific cognitive skills. Some authors contend that natural selection, operating at the individual level, is sufficient to account for the evolution of cooperation and morality (Baumard et al., 2013). From this perspective, humans moved into a niche where more prosocial individuals had a fitness advantage over others, arguably because they were desirable partners in the market of cooperation. A second possibility is that early groups of *Homo* that were comprised of a greater share of prosocial individuals were more prosperous than others, and that cooperation evolved through the mechanism known as group selection (Bowles and Gintis, 2011). Individual and group selection are not mutually incompatible, and both may have played a role in the evolution of human cooperation.

Although reconstructing the social life of extinct species is challenging, we now know enough about it to make an informed guess about when humans got rid of ape-like dominance hierarchies. The first point that we can make is that early *Homo* species, living roughly between 2.5 and 1.5 million years ago, had departed from the typical ape niche and adopted a more cooperative way of life. This trend became even more pronounced during the long reign of *H. erectus*, spanning more than a million years. If ape-like dominance hierarchies still existed during this long period, it must have been in a diminished form. That being said, the level of cooperation observed over the last 300,000 years in late *H. erectus*, *H. heidelbergensis,* Neandertal, and early *H. sapiens*—as is evidenced by their changing life histories, the adoption of large-game hunting, and the controlled use of fire—strikes me as entirely incompatible with the existence of dominance hierarchies, at least as they exist in ape societies. The cooperative skills of these human populations were clearly sufficient to keep would-be tyrants under control.

WHY HIERARCHIES ARE FUNCTIONAL

I have argued so far that dominance hierarchies are ubiquitous among social animals and result from increasingly well-understood neurological and behavioral mechanisms, as well as social dynamics. Although many of these mechanisms are present in our species, I explained that the comparison between human and animal hierarchies is often misleading. Indeed, humans have unique cognitive skills that support exceptional levels of cooperation and that have led in our evolutionary history to what Boehm (1999) calls "reversed dominance hierarchies," where uncooperative and aggressive bullies are pushed toward the bottom of hierarchies instead of rising to the top.

This account, however, raises further questions. The fact is that over the past 10,000 years or so most humans stopped living in relatively egalitarian foraging bands and were absorbed into increasingly large polities. They were brought—willingly or not—under the control of chiefs, kings, and presidents. Despite the success of some of these polities at maintaining relative equality between their subjects or citizens, the undisputable fact remains that most existing and past civilizations involved massive inequalities and forms of exploitation rarely seen in the animal kingdom. The existence of large-scale hierarchies as we know them raises an interesting scientific puzzle. How is it that humans—who, for most of their history, have been successful in tackling the ambitions of would-be alpha males—ended up creating forms of social organizations in which wealth and power is more often than not concentrated in the hands of the few? The question is the object of old controversies in philosophy, anthropology, and other social sciences. Why do chiefdoms and states exist? What are the origins of political power and domination?

Despite the variety of answers that these questions have received, two opposite views seem to have resisted the passage of time. The first contends that hierarchies exist because they yield collective benefits. Political centralization provides cooperation the scaffolding necessary to flourish beyond the foraging band. In philosophy, this view is generally associated with social contract theorists, such as Hobbes, Locke, and Rousseau. A similar perspective is also present in the more recent work of various social scientists inspired by functionalism and systems theory and, perhaps most prominently, those of Talcott Parsons (1966) and Elman Service (1962). The latter proposed an influential typology of "stages" in the evolution of human societies (from bands to tribes, chiefdoms, and states), with each stage leading to larger polities and more centralized leadership. A second view on the origin of hierarchies is that they result primarily from strategies of aggrandizing rulers, mindful of their own interests. This view is associated with the works of Marxist authors, including most prominently, Friedrich Engels (1884), and also with the classical work of Franz Oppenheimer (1972 [1908]), neo-evolutionary anthropologist Morton H. Fried (1967), and more recently, anthropologist Brian Hayden (2008, 2011).

I will call the first perspective the functionalist approach and the second the conflict-based approach to hierarchies. Economist Paul H. Rubin (2000) proposed a similar distinction when he opposed "dominance hierarchies," based on fear and exploitation, to "production hierarchies,"

supporting cooperation. At first sight both perspectives seem plausible. Anyone who has spent more than a week in a large organization will recognize that some form of hierarchical control is necessary for things to function. At the same time, the idea that leaders and rulers care more about their self-interest than about the well-being of their group or community sounds reasonable as well. I will argue that we do not have to choose between the functionalist and conflict-based approaches to hierarchies. As is often the case in the social sciences, a closer examination of the cognitive and behavioral mechanisms behind the phenomenon can help bridge the gap between the two positions (Bloch, 2013). My claim is that, given the nature of human cooperation, the creation of hierarchies is indeed a precondition to sustaining cooperation in very large groups, but that, depending on the form they take, hierarchies also create room for unprecedented exploitation.

Over the past decades, a large literature examined the dynamics of cooperation in the context of economic experiments (Fehr and Gächter, 2000; Camerer, 2003; Henrich et al., 2004; Gintis et al., 2006; Guala, 2012). This research established without any doubt that, under a broad range of circumstances, people are willing to incur some personal costs to punish unfair and opportunistic behavior and that this motivation is instrumental in supporting high levels of cooperation. For practical reasons, experimental research on cooperation focuses on the dynamics of small groups, where the behavior of individuals can be easily observed and measured. Research on small groups is crucial to understand the conditions under which people engage in cooperative ventures with colleagues, friends, and relatives. These are the most meaningful relationships we take part in, but they are not the only ones. Most of us are not afraid to take a walk alone at night because we know that police officers actively work to protect us. Most of us benefit every day from dozens of goods that would not exist if thousands of people—if not millions—across the world did not coordinate their actions through an amazing number of legal and economic arrangements. The crucial question is: why do we put our subsistence and well-being in the hands of people that we will never meet?

The question is relevant because the cooperative disposition we inherited from our foraging ancestors, although in many ways impressive, is also severely limited. We love to cooperate, but our prosocial motivations rapidly vanish when others deceive us or take advantage of us. Moreover, we are inclined to do less than our share as soon as we can do so without damaging our reputations (Kurzban, 2011; Pedersen et al., 2013). In daily face-to-face cooperation with our friends and colleagues, we overcome such limitations by keeping track of what others are doing. We make sure that everyone contributes to common goals and blame or shun free-riders when they fail to do so. But keeping score of everyone's actions becomes rapidly impracticable when cooperation involves too many people. Time is a scarce resource and much of it is needed to find out who did what to whom and under which circumstances. Gossip can provide information about people outside our immediate vicinity, but it is also time consuming and inefficient when too many people are concerned (Dunbar, 1996).

Cognitive limitations thus impose design constraints on the main institutions of human societies. For all time, meaningful cooperation between more than a few dozen people has depended on the presence of institutions that can, in one way or another, support trust between individuals that are not actively monitoring each other: trust that your colleagues in the other branches of the firm are doing their work, trust that the members of the other regiments are not deserting, trust that your follow citizens are paying their taxes and respecting the law, trust that the school personnel is taking care of your children, etc. Tribal systems, premodern states, modern governments, and large corporations have at least one design feature in common: they are all based on some form of grouping, in which the opinions and preferences of a representative reliably indicates the behavior of his peers, followers, or subordinates. Such groupings are extremely diverse—clans, lineages, societies, corporations, patronage networks, divisions, branches, departments, regiments, political parties, etc.—and can generally be treated as group agents, in the sense that they have a capacity to form beliefs and desires of their own, as well as to act upon those intentional states (List and Pettit, 2011). At the cognitive level, the creation of group agents is closely linked to the human social-cognitive capacity to create institutional facts (Dubreuil and Henshilwood, 2013; Tomasello, 2014).

In modern urban societies, large-scale cooperation is supported by complex group agents, such as governments and corporations, with long chains of command through which a CEO or a minister provides directives to senior managers, who in turn oversee the work of middle and lower management, who oversees the work of the rank and file. Management specialists study what they call "span of control," that is to say, the number of employees under the supervision of a manager in an organization (Keren and Levhari, 1979; Meier and Bohte, 2003; Topp and Desjardins, 2011). Optimal span of control, which makes the organization most efficient, is known to vary importantly depending on context. When work is highly routinized, a manager can supervise up to 25 employees without too much difficulty. But when work is more analytic in nature, a narrower span of control is needed, with a ratio that can go down to three to five employees per manager in information-rich environments. Variations in spans of control further suggest that managers are "nerve centers" who sustain trust across the organization by creating bridges between multiple "bands" (Mintzberg, 1971).

The creation of group agents to support large-scale cooperation is not specific to modern societies. Ethnographies of the most egalitarian hunters-gatherers, horticulturalists, and agriculturalists reveal that clans (or other kindred structure) play a central role in the establishment of alliances and exchange networks between bands, settlements, or villages. Thanks to their existence, individuals do not have to track the deeds of every person they might interact with and can focus on the reputation of a few group agents: which clan is reliable when it comes to paying the bride price or the wergild, partaking in raids against neighboring tribes or contributing to public work projects.

Group agents are necessary for large-scale cooperation to flourish, but they can take wildly different forms. The most prominent distinction concerns the way they make decisions. On the one hand, there are groups where everyone has her say and decisions are made mostly consensually. On the other hand, there are groups where one or a few individuals make decisions that they impose on subordinates. Let's call the first form of decision making "collegial" and the second "autocratic" (and let us acknowledge that there is a continuum between the two models). Autocratic and collegial decision making can both predominate in one society, just as they can coexist under various forms. For instance, traditional chiefdoms and premodern states are autocratic, but generally coexist with institutions like kindred structures, age grades, corporations, or secret societies, in which decision making can be more collegial. Similarly, modern governments and large corporations are structured mostly autocratically but coexist with a vast array of associations where individuals have more or less of an equal say. Even smaller work units within large hierarchical organizations generally have some room for collegial decision making (in fact, a general trend in management science over the past decades has been to emphasize the importance of fostering some form of collegiality in large organizations in order to empower employees and support their engagement).

Collegial and autocratic models have strongly divergent implications for the organization of cooperation. I want to mention two: the costs of decision making and the alignment of individual motivations with group decision, what List and Pettit (2011) call "incentive compatibility."

- *Costs of decision making*: Under the collegial approach, decision making is time consuming. Long discussions are needed to reach consensus. By contrast, autocratic decision making can go quickly (to fully appreciate the point, compare decision making by an academic department and by an army regiment).
- *Alignment of individual motivations*: Under the collegial model, securing individual motivation to comply with group decisions is typically easier, because everyone takes part in the decision. The situation is more complex under the autocratic approach, where individuals do not have their say.

Understanding the costs and benefits of both models is crucial in explaining why hierarchies exist among humans and what form they take. In many circumstances of social life, collegiality is an obvious choice. It works especially well among small groups, when there is no pressing need to make critical decisions or when individuals' beliefs and interests are well aligned with one another. This is generally the case within the household, within friend networks, or within small work units in larger organizations. By contrast, collegiality becomes ineffective when too many people are concerned, when urgent decisions must be made, and when opinions are too divergent.

More autocratic decision making addresses the problems of collegiality, but comes with its own challenge. Indeed, people need good reasons to comply with decisions they did not contribute to making. Generally, this good reason is some form of material compensation. Throughout history, autocratic decision making appears when leaders have the capacity to redistribute wealth and gifts of all sorts to secure the compliance of their subordinates (Earle, 1997; Trigger, 2003; Hayden and Villeneuve, 2011). This is the case with "big men" in traditional societies, chiefs in so-called complex chiefdoms, and aristocrats and kings in both premodern and modern states. This is also the case with managers in modern firms or government, where subordination to a chain of command is a condition of employment. Autocratic decision making typically persists as long as subordinates depend on rulers for their subsistence and well-being. This reality imposes a constraint on the expansion of autocratic group agents, which is limited by the capacity of leaders to extract resources and turn followers into subordinates.

FROM COOPERATIVE TO EXPLOITATIVE HIERARCHIES

The discussion outlined in the previous section clearly has a functionalist flavor. My claim is that, without hierarchies, large-scale cooperation would be impossible. Several people, however, are not satisfied with a purely functionalist explanation of hierarchies. It is easy to understand why. Chiefdoms, states, and other large organizations often involve such dramatic forms of violence, mistreatment, and injustice that it is hard to deny that not everyone benefits from them. From the perspective of a slave, a serf, or a member of a subordinate cast, hierarchies are more about exploitation than cooperation. My claim is that both the functionalist and conflict-based approaches capture part of the truth about hierarchies. In this section, I present three of the main reasons why hierarchies, although functional in

some sense, are not always equally functional for everyone (and sometimes even at the source of massive violence and abuse).

The first reason is linked to the very nature of human hierarchies. Leaders, even when they are constrained by collegiality, can draw some advantages from their position: prestige, credibility, discretionary control over resources, access to privileged information or contact networks, etc. The most egalitarian nonstate societies have rules and strategies to ensure that these advantages remain limited (Clastres, 1989; Boehm, 1999, 2012). Norms against polygyny, ostentatious displays of wealth, debt bondage, or slavery, for instance, help restrain the power of chiefs. In Iroquois society, for example, chiefs could capture slaves during raids against neighboring tribes, but after a few months, these slaves had to either be adopted into an Iroquois family (replacing a deceased person) or tortured to death. As a result, ambitious leaders could not accumulate large numbers of slaves that they could then use as a power basis to dominate the rest of their community (Viau, 1997). But even under the best circumstances, controlling leaders and rulers in a hierarchical context presents challenges. As the organization grows, members lose the capacity to track the behavior of their superiors directly and might start suspecting that the latter are taking advantage of their position (which may or may not be true). The challenge can never be fully eradicated in a world in which time is a scarce resource, although attempts can be made to minimize it. (In fact, a central objective of extremely popular leadership studies is to identify ways in which leaders of large organizations can build trust and keep their base engaged.)

I have argued elsewhere (Dubreuil, 2010a) that the main determinant of exploitative relationships is not the presence of hierarchies per se, but the existence of strong relationships of debt and dependence between leaders and their subordinates. The argument is that, once subordinates become highly dependent on leaders, they lose the capacity to exert an ethical check on them. The centrality of debt and dependence in the emergence of domination is a classical theme in political philosophy. It is ubiquitous in the work of Machiavelli, but was never so clearly described as in La Boétie's (2012 [1549], p. 30) *Discourse on Voluntary Servitude*:

> *There have always been five or six who had the tyrant's ear, and have gotten there by themselves or else were called by him to be accomplices in his cruelties and companions in his pleasures, to pander to his lusts and share in the goods he pillages. These six manage their chief so well that, out of solidarity, he has to be wicked not only for his own wickedness but also for theirs. These six have six hundred who profit under them and they do to their six hundreds what the six to do the tyrant. These six hundred hold under themselves six thousand whom they have raised up in state, to whom they grant either the governing of provinces of the handling of funds, so they will have a hand in their rapacity and cruelty and carry it out when the time comes, and otherwise do so much evil that they can only endure in their shadow, and be exempt from the law and punishment through them.*

La Boétie's description can be linked to my argument earlier regarding autocratic decision making. Autocracy reduces the cost of decision making, which explains why it can emerge in the first place. But to impose themselves, autocratic rulers need to make sure that the preferences of their subordinates align with theirs, which typically necessitates the transfer of a large number of resources and privileges. These transfers, in turn, make subordinates dependent on their rulers (through the system so brilliantly described by La Boétie) and unlikely to bite the hand that feeds them. In some circumstances, these mechanisms can lead to a vicious circle of growing oppression. The more the rulers and their subordinates oppress the masses to extract resources, the more they fear losing power and, as a result, the more they oppress the masses to extract more resources to consolidate their oppression (Fig. 29.1). Typically, oppressive systems collapse when rulers become unable to find the resources they need to support the loyalty of their subordinates, provoking defection in the ruling elites and the creation of new alliances with formerly excluded political actors (Tilly, 2004, 2007).

The role of debt and dependence in the emergence of exploitative hierarchies is a common theme in anthropology and archeology. In his classical work on Highland Burma, for instance, Edmund Leach (1954) describes the fluctuation between two types of political structures, one where power is in the hands of a single chief with loyal subordinates and the other, more republican, where a balance of power exists between different clans. A similar distinction is at the foundation of the dual-processual

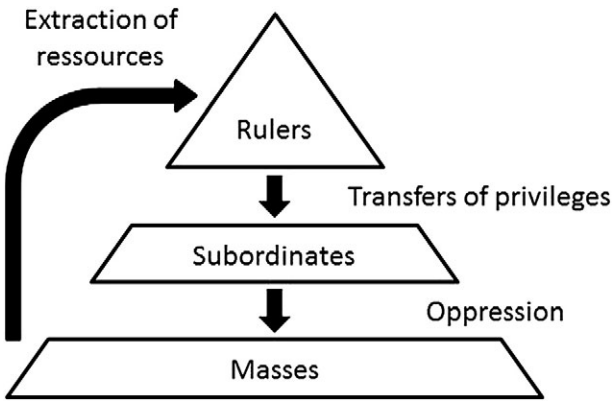

FIGURE 29.1 The dynamics of oppression.

theory in archeology (Blanton et al., 1996) that distinguishes two paths leading to complexity: one in which political power is based on the personal networks of aggrandizing leaders, the other where it rests on the equilibrium between corporate groups. These accounts can be linked to the distinction proposed earlier between collegial and autocratic decision making. Earle (1997), Testart (2004a,b, 2013), and Hayden (2008, 2011) have also provided detailed arguments concerning the role of wealth, ostentatious gift-giving, slavery, and debt bondage in securing the types of personal dependence at the origins of inequality and exploitation. Various strategies can be developed by subordinates to resist exploitation when hierarchies are based on strong relationships of dependence, including playing one chief against the other (Hayden and Villeneuve, 2011) or withdrawing cooperation and insulating oneself from rulers, as lower status groups often do in undemocratic states (Tilly, 2007).

The third reason why hierarchies, while in some sense functional, often lead to injustice and exploitation is found in our psychological reactions to inequalities between groups. Sidanius and Pratto (1999) developed the concept of social dominance to refer to the nexus of psychological mechanisms activated when a group is perceived as having higher status, prestige, and power. There is strong evidence that hierarchies trigger asymmetric behavioral responses among high-status and low-status groups. While in-group favoritism predominates among members of dominant groups, out-group favoritism is often observed among members of subordinate groups. For instance, members of low-status groups tend to perceive themselves and their peers as less competent and less deserving than members of high-status groups. As a consequence, emphasizing the lower status of a group can lead its members to adopt self-defeating behavior that reinforces the very negative stereotypes from which they suffer. Such behavioral asymmetries are particularly well documented in the case of African Americans, but seem to be a central feature of all relationships between groups of unequal status. A related phenomenon is known as social justification and is associated with research conducted by John Jost et al. (2009). The phenomenon refers to people's tendency to justify and legitimize the system in place, independently of how political and economic power is distributed within it. Such a tendency is widely documented, not only among those who take advantage of the system, but also among underprivileged groups. It is true that, other things being equal, slaves, members of low castes, proletarians, and subordinate ethnic groups do not support existing social arrangements as much as members of high-status groups, but they nevertheless present a strong bias in favor of the status quo even when it becomes manifestly unfavorable to them.

It is not entirely clear why exploited and underprivileged social groups have a bias in favor of existing hierarchies, but a plausible explanation can be found in Leon Festinger's (1957) theory of cognitive dissonance, according to which people experience psychological discomfort when they hold conflicting mental states. Indeed, the presence of strong inequalities and exploitative social arrangements can produce a conflict in subordinate groups between the frustration of being disadvantaged and the conviction that the system cannot be altered. Psychologist Susan Fiske (2011, p. 67) describes this tension in the following way:

> *Low-status groups face a conflict between favoring their in-group and living within a system that devalues it, so they show more ambivalence toward their own group than high-status people show toward theirs. The more low-status groups view hierarchy as inevitable, the worse is this internal conflict between valuing their group and acknowledging society's contempt for it.*

Reframing the situation and representing social arrangements as fair does not improve the material conditions of underprivileged groups, but can relieve the significant displeasure resulting from cognitive dissonance.

The concepts of social dominance and system justification do not explain why marked group-based inequalities became so important with the centralization of political power (while they were much more limited among our foraging ancestors), but they partly explain why exploitative social arrangements often persist and remain unchallenged by those who suffer under them.

CONCLUSION

This chapter aimed at providing a general overview of the diversity of social hierarchies in human populations. I had no intention of being exhaustive, as literally thousands of books—in virtually all disciplines in the humanities, the social sciences, and the life sciences—have been written on one aspect or another of this question. My objective was more modest: to provide a broad overview of the main mechanisms behind the creation of hierarchies in humans. I have shown that these mechanisms operate at various levels (biological, psychological, and social) and interact with one another to produce myriad outcomes. From mostly egalitarian foraging bands to large repressive regimes, as well as from small despotic chiefdoms to large democratic states, formal and institutionalized hierarchies often coexist with informal ones, and both can have wide-ranging influences on people's attitudes, behaviors, beliefs, well-being, health, fertility, and countless other variables.

My argument was broad, but can be summarized in a few key points:

- Social animals benefit from living in groups but are also in competition with one another when it comes to

feeding and mating. Dominance hierarchies are the outcome of an animals' interest in having privileged access to resources and mating opportunities, but also of avoiding aggression and maintaining relatively peaceful relationships with their conspecifics. The formation of hierarchies is influenced by several variables, including individual attributes, environmental factors, and social dynamics within groups.

- The basic mechanisms supporting an animal's drive to dominance are also present in humans and their effects can be observed in multiple ways. Nevertheless, humans do not form dominance hierarchies in the way that primates do. Their unequaled capacity for cooperation, rooted in unique social-cognitive skills and prosocial motivations, gives them the capacity to collectively resist potential alpha males.
- Control over aggressive and antisocial individuals is ubiquitous in small foraging bands and was the norm before the Neolithic. It appeared gradually during the long evolution of the genus *Homo*, supported by changes in human social cognition. In all likelihood, ape-like dominance hierarchies disappeared some hundreds of thousands of years ago and were absent in *H. heidelbergensis*, Neandertals, and early *H. sapiens.*
- Humans are experts at cooperating, but face significant difficulty when they try to extend cooperation beyond a few dozen individuals. Because of their limited capacity to monitor what people are doing, they need to design hierarchical institutions—based on collective agents with a reputation of their own—to maintain trust in large-scale cooperative networks. Some collective agents make decisions collegially, which is time consuming but helps to secure legitimacy, whereas others do it autocratically, which is more efficient but requires resources to secure the alignment of individual motivations with rulers' decisions.
- Hierarchies are functional in that their existence is a precondition of large-scale cooperation. On the other hand, they can easily lead to forms of inequality, exploitation and mistreatment unobserved in the animal kingdom. Exploitative hierarchies develop for a number of reasons, but most notably when subordinates depend on rulers for their well-being and have no incentive to exert an ethical check on them. Once in place, exploitative hierarchies persist partly because underprivileged and exploited groups are biased in favor of the status quo, even when they suffer from it.

The account proposed in this chapter provides no roadmap to the abolition of exploitation and injustice, but the mechanisms it described should be of interest to anyone who wishes to transform hierarchies we are a part of to promote greater respect, equality, and cooperation. There is no question that securing the subsistence and well-being of billions of people does and will continue to require high levels of cooperation. Humanity will not return to hunting and gathering and, in this sense, there are no alternatives to hierarchies. Nevertheless, an understanding of the mechanisms behind them can explain why they can be poorly designed and how they can be changed for the better.

REFERENCES

Abbott, D.H., Keverne, E.B., Bercovitch, F.B., et al., 2003. Are subordinates always stressed? A comparative analysis of rank differences in cortisol levels among primates. Hormones and Behaviour 43 (1), 67–82.

Adler, N.E., Epel, E.S., Castellazzo, G., Ickovics, J.R., 2000. Relationship of subjective and objective social status with psychological and physiological functioning: preliminary data in healthy white women. Health Psychology 19, 586–592.

Archie, E.A., Altmann, J., Alberts, S.C., 2012. Social status predicts wound healing in wild baboons. PNAS 109 (23), 9017–9022.

Argyle, M., 1994. The Psychology of Social Class. Routledge, New York.

Baron-Cohen, S., Leslie, A.M., Frith, U., 1985. Does the autistic child have a "theory of mind"? Cognition 21 (1), 37–46.

Batson, D., 2011. What's wrong with morality? Emotion Review 3, 230–235.

Baumard, N., 2016. The Origins of Fairness: How Evolution Explains Our Moral Nature. Oxford University Press, Oxford.

Baumard, N., 2010. Has punishment played a role in the evolution of cooperation? A critical review. Mind and Society 9 (2), 171–192.

Baumard, N., André, J.B., Sperber, D., 2013. A mutualistic theory of morality: the evolution of fairness by partner choice. Behavioral and Brain Sciences 36 (1), 59–78.

Beehner, J.C., Bergman, T.J., Cheney, D.L., Seyfarth, R.M., Whitten, P.L., 2006. Testosterone predicts future dominance rank and mating activity among male chacma baboons. Behavioral Ecology and Sociobiology 59, 469–479.

Beeman, E.A., 1947. The relation of the interval between castration and 1st encounter to the aggressive behavior of mice. Anatomical Record 99, 570–571.

Betzig, L., 1993. Sex, succession, and stratification in the first six civilizations: how powerful men reproduced, passed power on to their sons, and used power to defend their wealth, women and children. In: Ellis, L. (Ed.), Social Stratification and Socioeconomic Inequality, vol. 1. Praeger, New York, pp. 37–74.

Blanton, R., Feinman, G., Kowalewski, S., Peregrine, P., 1996. A dual-processual theory for the evolution of mesoamerican civilization. Current Anthropology 37 (1), 1–14.

Bloch, M., 2013. Anthropology and the Cognitive Challenge. Cambridge University Press.

Boehm, C., 1993. Egalitarian behavior and reverse dominance hierarchy. Current Anthropology 34 (3), 227–254.

Boehm, C., 1999. Hierarchy in the Forest. Harvard University Press, Cambridge.

Boehm, C., 2012. Moral Origins: The Evolution of Virtue, Altruism, and Shame. Basic Books, New York.

Booth, A., Granger, D., Mazur, A., Kivlighan, K., 2006. Testosterone and social behavior. Social Forces 85, 167–191.

Bowles, S., Gintis, H., 2011. The Cooperative Species. Princeton University Press, Princeton.

Buss, D.M., 2007. Evolutionary Psychology: The New Science of the Mind. Omegatype Typography, Inc., Boston.

Call, J., Hare, B., Carpenter, M., Tomasello, M., 2004. "Unwilling" versus "unable": chimpanzees understanding of human intentional action. Developmental Science 7, 488–498.

Camerer, C., 2003. Behavioral Game Theory: Experiment in Strategic Interactions. Princeton University Press, Princeton.

Caron, F., d'Errico, F., Del Moral, P., Santos, F., Zilhão, J., 2011. The reality of Neandertal symbolic behavior at the Grotte du Renne, Arcy-sur-Cure. PLoS One 6 (6), e21545.

Case, A., Paxson, C., 2008. Stature and status: height, ability, and labor market outcomes. Journal of Political Economy 116, 499–532.

Chase, I.D., Tovey, C., Spangler-Martin, D., Manfredonia, M., 2002. Individual differences versus social dynamics in the formation of animal dominance hierarchies. PNAS 99, 5744–5749.

Christiansen, K., 1998. Behavioural correlates of testosterone. In: Nieschlag, E., Behre, H.M. (Eds.), Testosterone: Action, Deficiency, Substitution. Springer, Berlin, pp. 125–172.

Clastres, P., 1989. Society Against the State. Zone Books, New York.

Clavien, C., Klein, R., 2010. Eager at fairness or for revenge? Psychological altruism in economics. Economics and Philosophy 26 (3), 267–290.

Clutton-Brock, T.H., 1988. Reproductive success. In: Clutton-Brock, T.H. (Ed.), Reproductive Success. University of Chicago Press, Chicago, pp. 472–486.

Cohen, S., Alper, C.M., Doyle, W.J., et al., 2008. Objective and subjective socioeconomic status and susceptibility to the common cold. Health Psychology 27 (2), 268–274.

Cummins, D.D., 2005. Dominance, status, and social hierarchies. In: Buss, D.M. (Ed.), The Handbook of Evolutionary Psychology. Wiley, Hoboken, NJ, pp. 676–697.

Dabbs Jr., J.M., 1992. Testosterone and occupational achievement. Social Forces 70, 813–824.

Dabbs Jr., J.M., Carr, T.S., Frady, R.L., Riad, J.K., 1995. Testosterone, crime, and misbehavior among 692 male prison inmates. Personality and Individual Differences 18 (5), 627–663.

Dabbs Jr., J.M., Bernieri, F.J., Strong, R.K., Campo, R., Milun, R., 2001. Going on stage: testosterone in greetings and meetings. Journal of Research in Personality 35, 27–40.

Dabbs Jr., J.M., Hargrove, M.F., 1997. Age, testosterone, and behavior among female prison inmates. Psychosomatic Medecine 59 (5), 477–480.

Dubreuil, B., 2015. Anger and morality. Topoi 34 (2), 475–482.

Dubreuil, B., 2010a. Human Evolution and the Origins of Hierarchies. Cambridge University Press, Cambridge.

Dubreuil, B., 2010b. Paleolithic public goods games: why human cooperation and culture did not evolve in one step. Biology and Philosophy 25 (1), 53–73.

Dubreuil, B., Henshilwood, C., 2013. Material culture and language. In: Lefebvre, C., Comrie, B., Cohen, H. (Eds.), New Perspectives on the Origins of Language. John Benjamins Publishing Company.

Dunbar, R., 1996. Grooming, Gossip and the Evolution of Language. Harvard University Press.

Earle, T., 1997. How Chiefs Come to Power: The Political Economy in Prehistory. Stanford University Press.

Ellis, L., 1995. Dominance and reproductive success among nonhuman animals: a cross-species comparison. Ethology & Sociobiology 16, 257–333.

Engels, F., 1884. The Origin of the Family, Private Property, and the State: In the Light of the Researches of Lewis H. Morgan. Penguin Classics.

Fehr, E., Gächter, S., 2000. Cooperation and punishment in public goods experiments. American Economic Review 90 (4), 980–994.

Fessler, D., Haley, K., 2003. The strategy of affect: emotions in human cooperation. In: Hammerstein, P. (Ed.), The Genetic and Cultural Evolution of Cooperation. MIT Press, Cambridge.

Festinger, L., 1957. A Theory of Cognitive Dissonance. Stanford University Press, California.

Fieder, M., Suber, S., Bookstein, F.L., 2011. Socioeconomic status, marital status and childlessness in men and women: an analysis of census data from six countries. Journal of Biosocial Science 43, 619–635.

Fisek, M.H., Ofshe, R., 1970. The process of status evolution. Sociometry 33, 327–346.

Fiske, S.T., 2011. Envy Up, Scorn Down: How Status Divides Us. Russell Sage Foundation, New York.

Flavell, J., Flavell, E., Green, F., 1983. Development of the appearance-reality distinction. Cognitive Development 15, 95–120.

Fried, M.H., 1967. The Evolution of Political Society an Essay in Political Anthropology. Random House, New York.

Friedman, M., 1996. Type a Behavior: Its Diagnosis and Treatment. Plenum Press, New York.

Gesquiere, L.R., Learn, N.H., Simao, C.M., et al., 2011. Life at the top: rank and stress in wild male baboons. Science 333, 357–360.

Gintis, H., Bowles, S., Boyd, R., Fehr, E. (Eds.), 2006. Moral Sentiments and Material Interests. MIT Press, Cambridge, MA.

Green, R.E., Krause, J., Briggs, A.W., et al., 2010. A draft sequence of the Neandertal genome. Science 328 (5979), 710–722.

Greene, J., 2013. Moral Tribes: Emotion, Reason, and the Gap Between Us and Them. The Pinguin Press, New York.

Guala, F., 2012. Reciprocity: weak or strong? What punishment experiments do (and do not) demonstrate. Behavioral and Brain Science 35, 1–59.

Gurven, M., 2004. To give or to give not: an evolutionary ecology of human food transfers. Behavioral and Brain Sciences 27, 543–583.

Haidt, J., 2003. The moral emotions. In: Davidson, R., Scherer, K., Goldsmith, H. (Eds.), Handbook of Affective Sciences. Oxford University Press, Oxford.

Haidt, J., 2012. The Righteous Mind: Why Good People Are Divided by Politics and Religion. Pantheon Books, New York.

Hare, B., Call, J., Agnetta, B., Tomasello, M., 2000. Chimpanzees know what conspecifics do and do not see. Animal Behaviour 59, 771–786.

Hawley, P., 1999. The ontogenesis of social dominance: a strategy-based evolutionary perspective. Developmental Review 19, 97–132.

Hayden, B., 2008. L'homme et l'inégalité: L'invention de la hiérarchie pendant la préhistoire. CNRS Éditions, Paris.

Hayden, B., 2011. Big man, big heart? The political role of aggrandizers in egalitarian and transegalitarian societies. In: Forsyth, D., Hoyt, C. (Eds.), For the Greater Good of All: Perspectives on Individualism, Society, and Leadership, pp. 101–118.

Hayden, B., Villeneuve, S., 2011. A century of feasting studies. Annual Review of Anthropology 40, 433–449.

Henrich, J., Bowles, S., Boyd, R., Camerer, C., Fehr, E., Gintis, H., 2004. Foundations of Human Sociality: Economic Experiments and Ethnographic Evidence From Fifteen Small-scale Societies. Oxford University Press, Oxford.

Henrich, J., Gil-White, F., 2001. The evolution of prestige: freely conferred deference as a mechanism for enhancing the benefits of cultural transmission. Evolution and Human Behavior 22, 165–196.

Henshilwood, C., Dubreuil, B., 2011. The still Bay and Howiesons Poort, 77–59 ka: symbolic material culture and the evolution of the mind during the African middle stone age. Current Anthropology 52 (3), 361–400.

Hirschenhauser, K., Taborsky, M., Oliveira, T., Canàrio, A.V.M., Oliveira, R.F., 2004. A test of the "challenge hypothesis" in cichlid fish: simulated partner and territory intruder experiments. Animal Behaviour 68 (4), 741–750.

Hublin, J.-J., Neubauer, S., Gunz, P., 2015. Brain ontogeny and life history in Pleistocene hominins. Philosophical Transactions of the Royal Society B 370 (1663).

Johnson, S.L., Leedom, L.J., Muhtadie, L., 2012. The dominance behavioral system and psychopathology: evidence from self-report, observational, and biological studies. Psychological Bulletin 138 (4), 692–743.

Jost, J.T., Kay, A.C., Thorisdottir, H. (Eds.), 2009. Social and Psychological Bases of Ideology and System Justification. Oxford University Press, New York.

Kalma, A., 1991. Hierarchisation and dominance assessment at first glance. European Journal of Social Psychology 21 (2), 165–181.

Kaplan, H.S., Hill, K.R., Lancaster, J., Hurtado, A.M., 2000. A theory of human life history evolution: diet, intelligence, and longevity. Evolutionary Anthropology 9, 156–185.

Kelly, R.L., 1995. The Foraging Spectrum: Diversity in Hunter-Gatherer Life Ways. Smithsonian Institution, Washington.

Keren, M., Levhari, D., 1979. The optimum span of control in a pure hierarchy. Management Science 25 (11), 1162–1172.

Kroeber, A.L., Kluckhohn, C., 1952. Culture: A Critical Review of Concepts and Definitions. Harvard University Peabody Museum of American Archeology and Ethnology. Papers 47.

Kurzban, R., 2011. Why Everyone (Else) Is a Hypocrite: Evolution and the Modular Mind. Princeton University Press, Princeton.

de La Boétie, E., 2012 [1549]. Discourse on Voluntary Servitude. Hackett Publishing Compagny.

Laland, K.N., Galef, B.G., 2009. The Question of Animal Culture. Harvard University Press, Cambridge, MA.

Leach, E., 1954. Political System of Highland Burma. Harvard University Press, Cambridge, MA.

Lee, R.B., Daly, R. (Eds.), 1999. The Cambridge Encyclopedia of Hunters and Gatherers. Cambridge University Press, Cambridge.

List, C., Pettit, P., 2011. Group Agency: The Possibility, Design and Status of Corporate Agents. Oxford University Press, Oxford.

Maccoby, E.E., 1990. Gender and relationships: a developmental account. American Psychologist 45, 513–520.

Manogue, K., Leshner, A., Candland, D., 1975. Dominance status and adrenocortical reactivity to stress in squirrel monkeys (*Saimiri sciureus*). Primates 16, 457–463.

Marmot, M.G., Smith, G.D., Stansfeld, S., et al., 1991. Health Inequalities among British civil servants: the Whitehall II study. Lancet 337 (8754), 1387–1393.

Martin, G.B., Clark, R.D., 1982. Distress crying in neonates: species and peer specificity. Developmental Psychology 18, 3–9.

Mazur, A., Booth, A., 1998. Testosterone and dominance in men. Behavioral and Brain Sciences 21, 353–363.

McEwen, B.S., Lasley, E.N., 2002. The End of Stress as We Know It. Joseph Henry Press, Washington, DC.

McHenry, H.M., Coffing, K., 2000. Australopithecus to Homo: transformations in body and mind. Annual Review of Anthropology 29, 125–146.

Meier, K.J., Bohte, J., 2003. Span of control and public organizations: implementing luther gulick's research design. Public Administration Review 63 (1), 61–70.

Mikhail, J., 2010. Elements of Moral Cognition: Rawls Linguistic Analogy and the Cognitive Science of Moral and Legal Judgment. Cambridge University Press, Cambridge.

Mintzberg, H., 1971. Managerial work: analysis from observation. Management Science 18 (2), B97–B110.

Moskowitz, D.S., 1993. Dominance and friendliness: on the interaction of gender and situation. Journal of Personality 61, 387–409.

Muehlenbein, M.P., Watts, D.P., Whitten, P., 2004. Dominance rank and fecal testosterone levels in adult male chimpanzees (Pan troglodytes schweinfurthii) at Ngogo, Kibale National Park, Uganda. American Journal of Primatology 64, 71–82.

Mueller, A., Mazur, A., 1996. Facial dominance of West Point cadets as a predictor of later military rank. Social Forces 74, 823–850.

Muller, M.N., Wrangham, R.W., 2004. Dominance, aggression and testosterone in wild chimpanzees: a test of the "challenge hypothesis". Animal Behaviour 67 (1), 113–123.

Onishi, K., Baillargeon, R., 2005. Do 15-month-old infants understand false beliefs? Science 308, 255–258.

Oppenheimer, F., 1972 [1908]. The State: Its History and Development Viewed Sociologically. Arno Press, New York.

Parsons, T., 1966. Societies: Evolutionary and Comparative Perspectives. Prentice-Hall, Inc., Englewood Cliffs, NJ.

Pedersen, E., Kurzban, R., McCullough, M., 2013. Do humans really punish altruistically? A closer look. Proceedings of the Royal Society B 280 (1758), 2012–2723.

Pellegrini, A.D., Roseth, C.J., Mliner, S., et al., 2007. Social dominance in preschool classrooms. Journal of Comparative Psychology 121 (1), 54–64.

Perner, J., Stummer, S., Sprung, M., Doherty, M., 2002. Theory of mind finds its Piagetian perspective: why alternative naming comes with understanding belief. Cognitive Development 17, 1451–1472.

Portera, C.C., Marlowe, F.W., 2007. How marginal are forager habitats? Journal of Archaeological Science 34 (1), 59–68.

Prinz, J., 2007. The Emotional Construction of Morals. Oxford University Press, Oxford.

Rakoczy, H., Warneken, F., Tomasello, M., 2008. The sources of normativity: young children's awareness of the normative structure of games. Developmental Psychology 44, 875–881.

Richards, M.P., Pettitt, P.B., Trinkaus, E., et al., 2000. Neanderthal diet at Vindija and Neanderthal predation: the evidence from stable isotopes. PNAS 97, 7663–7666.

Rightmire, G.P., 2004. Brain size and encephalization in early to mid-pleistocene homo. American Journal of Physical Anthropology 124, 109–123.

Rivers, J.J., Josephs, R.A., 2010. Dominance and Health: the role of social rank in physiology and illness. In: Guinote, A., Vescio, T.K. (Eds.), The Social Psychology of Power. Guilford Press, New York, pp. 87–112.

Robson, S.L., Wood, B., 2008. Hominin life history: reconstruction and evolution. Journal of Anatomy 212, 394–425.

Rodríguez-Vidal, J., d'Errico, F., Giles Pacheco, F., et al., 2014. A rock engraving made by Neanderthals in Gibraltar. PNAS 111, 13301–13306.

Rubin, P.H., 2000. Hierarchy. Human Nature 11 (3), 259–279.
Surian, L., Caldi, S., Sperber, D., 2007. Attribution of beliefs by 13-month-old infants. Psychological Science 18, 580–586.
Sapolsky, R.M., 1993. The physiology of dominance in stable versus unstable social hierarchies. In: Mason, W., Mendoza, S.P. (Eds.), Primate and Social Conflict. State University of New York Press, Albany, pp. 171–204.
Sapolsky, R.M., 2004a. Social status and health in humans and other animals. Annual Review of Anthropology 33, 393–418.
Sapolsky, R., 2004b. Why Zebras Don't Get Ulcers: The Acclaimed Guide to Stress, Stress-related Diseases, and Coping. Henry Holt and Company, New York.
Sapolsky, R.M., 2005. The influence of social hierarchy on primate health. Science 308, 648–652.
Schjelderup-Ebbe, T., 1922. Beiträge zur sozialpsychologie des haushuhns. Zeitschrift für Psychologie 88, 225–252.
Schmidt, M.F.H., Tomasello, M., 2012. Young children enforce social norms. Current Directions in Psychological Science 21 (4), 232–236.
Schmitt, A., Atzwanger, K., 1995. Walking fast-ranking high: a sociobiological perspective on pace. Ethology and Sociobiology 16, 451–462.
Searle, J., 1995. The Construction of Social Reality. The Free Press, New York.
Service, E.R., 1962. Primitive Social Organization: An Evolutionary Perspective. Random House, New York.
Setchell, J.M., Smith, T., Wickings, E.J., Knapp, L.A., 2010. Stress, social behaviour, and secondary sexual traits in a male primate. Hormones and Behavior 58, 720–728.
Sidanius, J., Pratto, F., 1999. Social Dominance: An Intergroup Theory of Social Hierarchy and Oppression. Cambridge University Press, Cambridge.
Stanton, S.J., Beehner, J.C., Saini, E.K., Kuhn, C.M., LaBar, K.S., 2009. Dominance, politics, and physiology: voters' testosterone changes on the night of the 2008 United States Presidential election. PLoS One 4 (10), e7543.
Testart, A., 2004a. La Servitude Volontaire I: Les Morts D'accompagnement. Errance, Paris.
Testart, A., 2004b. La Servitude Volontaire II: L'origine de l'État. Errance, Paris.
Testart, A., 2013. Avant l'histoire. L'évolution des Sociétés de Lascaux à Carnac. Gallimard, Paris.
Thieme, H., 1997. Lower paleolithic hunting spears. Nature 385, 807–810.
Tilly, C., 2004. Contention & Democracy in Europe, 1650–2000. Cambridge University Press, Cambridge.
Tilly, C., 2007. Democracy. Cambridge University Press, Cambridge.
Tomasello, M., 2010. Origins of Human Communication. MIT Press, Cambridge, MA.
Tomasello, M., 2014. A Natural History of Human Thinking. Harvard University Press, Cambridge, MA.
Tomasello, M., Moll, H., 2013. Why don't apes understand false beliefs? In: Banaji, M.R., Gelman, S.A. (Eds.), Navigating the Social World: What Infants, Children, and Other Species Can Teach Us. Oxford University Press, Oxford, pp. 81–87.
Topp, K., Desjardins, J., 2011. Span of control: designing organizations for effectiveness. In: Wolf, J., Hanson, H., Moir, M. (Eds.), Organization Development in Healthcare, a Guide for Leaders. Information Age Publishing Inc., Charlotte, NC, pp. 211–230.
Trigger, B., 2003. Understanding Early Civilizations: A Comparative Study. Cambridge University Press, New York.
Ungar, P.S., Grine, F.E., Teaford, M.F., 2006. Diet in early homo: a review of the evidence and a new model of adaptive versatility. Annual Review Anthropology 35, 209–228.
Viau, R., 1997. Enfants du Néant et Mangeurs D'âmes: Guerre, Culture et Société en Iroquoisie Ancienne. Boréal, Montréal.
van Winden, F., 2007. Affect and fairness in economics. Social Justice Research 20 (1), 35–52.
de Waal, F., 1982. Chimpanzee Politics. Power and Sex among Apes. Jonathan Cape, London.
Warneken, F., Chen, F., Tomasello, M., 2006. Cooperative activities in young children and chimpanzees. Child Development 77 (3), 640–663.
Wimmer, H., Perner, J., 1983. Beliefs about beliefs: representation and constraining function of wrong beliefs in young children's understanding of deception. Cognition 13 (1), 103–128.
Wingfield, J.C., Hegner, R.E., Dufty, A.M., Ball, G.F., 1990. The "challenge hypothesis": theoretical implications for patterns of testosterone secretion, mating systems and breeding strategies. American Naturalist 136, 829–846.
Wingfield, J.C., Jacobs, J.D., Tramontin, A.D., et al., 2000. Toward an ecological basis of hormone-behavior interactions in reproduction of birds. In: Wallen, K., Schneider, J. (Eds.), Reproduction in Context. MIT Press, Cambridge, MA, pp. 85–128.
Yeh, S.-R., Fricke, R.A., Edwards, D.H., 1996. The effect of social experience on serotonergic modulation of the escape circuit of crayfish. Science 271 (5247), 366–369.
Zahn-Waxler, C., Radke-Yarrow, M., Wagner, E., Chapman, M., 1992. Development of concern for others. Developmental Psychology 28, 126–136.
Zerjal, T., Xue, Y., Bertorelle, G., et al., 2003. The genetic legacy of the Mongols. American Journal of Human Genetics 72 (3), 717–721.
Zilhão, J., 2012. Personal ornaments and symbolism among the Neanderthals. In: Elias, S. (Ed.), Origins of Human Innovation and Creativity, Developments in Quaternary Science, vol. 16. Elsevier, Amsterdam, pp. 35–49.

Chapter 30

Homosexuality and Evolution: A Critical Appraisal*

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INTRODUCTION

This chapter investigates human homosexuality from an evolutionary perspective. The chapter is broad in scope with three main sections. These consider (1) the extent of homosexuality both among animals and among humans in present and past cultures; (2) the structural correlates of human homosexuality in both genes and brain structure; and (3) theories for why human homosexuality has evolved.

To begin, a major issue is how homosexuality is defined. Indeed, is homosexuality a biological trait at all? Is it homosexuality when two men or two women gaze lovingly at each other across a crowded room, destined never to meet; when a married man with children assumes the superior position atop a willing, hairy, leather-bedecked partner; when a war lord rapes a male prisoner-of-war; when a teenage cabin boy services his ship's captain; when two men or two women partners of 30 years marry at their local place of worship? Is homosexuality some of these, all of these?

Researchers have devised many operational definitions for homosexuality including same-sex genital contact regardless of context or motivation, or a sense of personal identity revealed through interviews. Varied operational definitions of homosexuality affect the repeatability of biological studies of homosexuality.

Ancillary issues arise too. What evolutionary purpose do the external genitals serve? Is homosexual sex a misuse of these organs? Even the gonads, organs whose primary function is the production of gametes, have other functions, such as hormone secretion. What about the external genitals? Is their only purpose to serve as conduits for the heterosexual transfer and receipt of sperm?

Indeed, in mammals, genitals are often signaling organs. In humans, the signaling significance of genitals may underlie why pornography is provocative.

Moreover, the innervation of external genitals in mammals provides a highway to the brain's pleasure centers. Could the reciprocal pleasure from tactile stimulation of genitals in mammals be the counterpart of the reciprocal pleasure birds experience when mutually preening each other's feathers? Are studies of homosexuality missing the point? Perhaps we should be investigating reciprocal physical intimacy in general? Does focusing on reciprocal sexual pleasure while ignoring other forms of reciprocal physical pleasure represent a fetishizing of sex to the exclusion of other functionally equivalent behaviors?

And then there is gender. How many human genders exist? Two? No. India, Pakistan, Nepal, and Bangladesh have three. In these countries, the hijra, a cast-like group of male-to-female transgender people who number over five million members, are formally classified as a third gender on government documents. A sexually intimate relation between a hijra woman and her male husband might then be considered homosexual, yet also heterogenderal. Among animals too, many species have more than the two morphs associated with the male and female sexes. The multiple morphs, sometimes termed alternative mating strategies, amount to multiple genders of males and females, allowing for a network of same-sex, different-gender schemes of courtship, affiliation, and physical intimacy. Can an evolutionary theory of homosexuality ignore its intertwining with gender expression and identity?

An evolutionary theory of human homosexuality is thus a multifaceted enterprise. In the following pages, I will critically review studies that are relevant to one or more possible objectives of an evolutionary theory of human

* Because of its subject matter, the editors caution that some readers might find the language to be strong and the material to be graphic.

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00030-2

homosexuality. Some aspects of this review are partly condensed from Roughgarden (2004).

EXTENT OF HOMOSEXUALITY

This major section of the chapter considers the distribution of homosexuality among animals and across human cultures.

Animals

Fifteen years ago scientists were still in denial about how common homosexuality is among animals. By "homosexuality," for the moment I refer only to same-sex mounting regardless of context and mutual touching of genitals.

In 2000, George Barlow, about to retire, in a summary of his career's work on the biology of cichlid fish wrote, "When animals have access to members of the opposite sex, homosexuality is virtually unknown in nature, with some rare exceptions among primates."

Yet a year earlier, Bruce Bagemihl, out as gay and early in his career, published a 751-page book (Bagemihl, 1999) reviewing unforced same-sex genital contact in the wild in over 300 species of vertebrates. Bagemihl, at the time largely unknown to biologists, received his PhD in linguistics from the University of British Columbia. All his cases were drawn from the peer-reviewed scientific literature. Bagemihl's compilation was followed by another in 2006 (Sommer and Vasey, 2006).

Today, in 2016, the reality of extensive homosexuality among animals is generally accepted among biologists. The 300 known examples of homosexuality in animals, surely an underestimate, reveal much diversity: in some species only males are homosexual, in some only females, in others both sexes; in almost all the homosexuality is mixed in with heterosexuality by the same individual; in some species a small fraction participates in homosexuality; in others, like our closest relative, the bonobo chimpanzee, every animal does (Parish, 1996). Clearly, homosexuality among animals exhibits great contextual variation.

Rather than wondering why an animal is homosexual, the converse may be more interesting. Why is not every animal homosexual, perhaps mixed in with some minimal amount of heterosexuality to ensure reproduction? Indeed, the task of an evolutionary theory of homosexual behavior might be conceived as the need to explain a polymorphism: to account in each species for the ratio of those who do to those who do not employ homosexual behavior.

Homosexuality is widely distributed across many higher taxa and is especially well-documented in birds and mammals, and also in insects. This wide distribution implies that homosexuality has originated many times in the animal kingdom.

Concerning primates, their family tree indicates a pattern. From its base near the ground, the primate tree trunk splits first into the prosimians on one side and the anthropoids on the other side. The prosimian branch, including bush babies, lemurs, and tarsiers, appear to have only incidental same-sex mounting while in heat, and no evidence of a major social role for same-sex courtship. The anthropoid branch splits into two subbranches: the new world primates and the old world primates. The new world primates, including marmosets, tamarins, and the monkeys with prehensile tails, such as spider monkeys, do have some homosexual behavior. In the old world primates though, homosexual courtship becomes prominent. The old world primates, including the macaques (cheek pouch monkeys), baboons, gibbons, orangutans, gorillas, chimpanzees, bonobos, and humans, have the most sophisticated of the primate societies and also the most extensive homosexuality. In these societies, individuals form complex relationships with one another, relationships evidently fostered both with same-sex as well as between-sex sexuality (Vasey, 1995).

The pattern of occurrence of homosexuality across the primate family tree indicates that homosexuality in anthropoid primates, especially in the old world lineages, is an evolutionary innovation originating around 50 million - years ago when the prosimian and anthropoid lineages began their divergence.

Species with multiple genders of males and females are rather common. Documented examples include the North American bull frog, North American plainfin midshipman, and Pacific and Atlantic salmon: two male genders, one female gender; North American bluegill sunfish, spotted European wrasse, cichlid fish from Mozambique, and the Southwestern American tree lizard: three male genders, one female gender; Canadian white throated sparrow: two male genders, two female genders; Southwestern side blotched lizard: three male genders, two female genders, and many others (cf. review in Roughgarden, 2004, pp. 75−106).

In addition, transgender animals have been reported in detail for the sunangel hummingbirds of the Andes from Venezuela through Columbia, Ecuador, Peru, to Bolivia. Male sunangel hummingbirds have colorful feathers on their throats called a gorget. In these species, a "masculine female" is a female with the markings that a majority of the males possess, and a "feminine male" is male with the markings that a majority of the females possess. The investigation of masculine females and feminine males now encompasses 42 species of hummingbirds from five genera, yielding the statistical information about transgender expression in this entire groups of birds (Bleiweiss, 1992, 1999, 2001).

I note in passing that the variation in gender and sexuality now known throughout the animal kingdom and

especially well-documented in vertebrates, casts considerable doubt on the accuracy and usefulness of Darwin's (1871) theory of sexual selection. This area of evolutionary biology presents a binary male/female and strictly heterosexual picture of sex and gender roles as universally normal. The form that sexual theory's modification and/or replacement should take is hotly debated (see, eg, Roughgarden, 2004, 2009, 2015; Roughgarden et al., 2015).

Humans

Turning from animals to people, the subject of homosexuality moves beyond behavior to identity. Homosexuality did not become a category of personal identity until the mid-1800s.

Karl Kertbeny, a Hungarian-German author, published the term "homosexual" (in German) in 1869 and used the term, "heterosexual," in private correspondence the year before (Greenberg, 1988; Katz, 1995; Beachey, 2010). Before this, homosexuality did not exist as a category of personal identity, although ample reference is made to homosexual conduct in writings for many civilizations extending to ancient time.

A wealth of material from ancient Greece pertains to same-sex love and sexuality, including dialogues of Plato, such as the Symposium, plays by Aristophanes, and Greek artwork and vases (Dover, 1978; Halperin, 1990). Homosexual images are even found on European Mesolithic rock art (Nash, 2001). In India, the antecedents of today's third gender, the hijra, are featured in the Mahabharata, the Kama Sutra, and in some translations of the Ramayana. Signs of hijra extend to early, even prehistoric, periods of civilization as long ago as 2500 BCE (Zwilling and Sweet, 1996; Penrose, 2001). At more or less the same time, the galli or Cybelean priestesses represented a third gender group that originated in the Neolithic of Anatolia and later spread throughout the Roman empire (Roscoe, 1996; Doniger, 2009; Kueffler, 2001). Gender-variant homosexual people are well represented in the Bible too. Both the Hebrew and Christian Testaments refer at length to eunuchs. In Isaiah 56:3−5, eunuchs are welcomed into the temple. In Matthew 19:11−12, Jesus speaks approvingly of eunuchs, and in Acts 32-40, a eunuch is baptized (Jung and Coray, 2001; Jung and Vigen, 2010). The new world also featured gender-variant homosexual people, referred to as two-spirited or winkte (Williams, 1986; Roscoe, 1991, 1998), the muxe in Zapotec, Mexico, as well as the mahu, fa'afafine, and others throughout Polynesia (Herdt, 1994). Southeast Asia features the waria in Indonesia, the kathoey of Thailand, and the bissu, calabai, and calalai of Sulawesi, among others (Peletz, 2006). Indeed, collectively, the sum of all cultures, today and throughout history, reveal a seemingly endless number of native transgender categories. Moreover, those cultures in which gender identity is associated with genital morphology have an indigenous form of gender reassignment surgery, such as the nirvan among the hijra, whereas cultures that emphasize work and occupation as the marker of gender identity, such as the two-spirits, do not.

The reason why homosexuality did not exist as a category of personal identity even though homosexual activity and non-binary gender expressions have existed in the human species since prehistoric times is that the techniques of sexual activity, not the sexual identity of the partner, were socially regulated. For example, the famous injunction against homosexual activity from the Holiness Code in the Bible, "You shall not lie with a male as with a woman; it is an abomination" (Leviticus 18:22) specifically condemns sex in which one male partner penetrates the other, particularly anal sex. (Heterosexual sex featured frontal intercourse when seeking conception and anal intercourse when avoiding pregnancy.) In contrast, approved same-sex intercourse among the Greeks was the intercrural or inter-crotch position: the active partner thrusts his penis between the thighs of the passive partner just below the scrotum (Dover, 1978). I have termed this the "missionary position for gay male sex"; it satisfies the letter of the law in Leviticus because a man would not lie with a woman and use the intercrural position with her (Roughgarden, 2004).

Even today, some cultural traditions focus more on the techniques of same-sex activity than on the gender of the participants. For example, in India, kothis are an identity category of receptive partners in sexual encounters with men who are nonetheless considered heterosexual and who often have a wife and children (Chakrapani et al., 2007).

Thus, an evolutionary theory of homosexuality, what it needs to explain, is itself a cultural artifact. A Western perspective might demand an explanation of why same-sex genital contact behavior evolved. Elsewhere, an evolutionary theory of homosexuality might be called upon to explain why a male would assume the subordinate position in intercourse. When Western science purports to explain any deviation from "normal" human sexual conduct, the effort flies in the face of extensive cross-cultural variation in exactly what constitutes normal.

SUBSTANCE OF HOMOSEXUALITY

This major section of the chapter considers the structural correlates of homosexuality and gender identity. First, genes are discussed with respect to homosexuality, then brain structure is discussed separately with respect to homosexuality and to gender identity.

Gay Genes

Being gay and lesbian runs in families. If a man is straight, the chance is only 4% his brother is gay, the same percentage as in the general population. If a man is gay, the chance increases fivefold, to 22%, that his brother is gay or bisexual too. Whether a man is straight or gay has no statistical effect on whether his sister is straight or lesbian (Pillard and Weinrich, 1986). Similarly, if a woman is lesbian, her sister is about twice as likely also to be lesbian than if a woman is straight. Whether a woman is lesbian has a very small or undetectable statistical effect on whether her brother is gay or straight (Bailey and Benishay, 1993; Bailey and Bell, 1993; Dawood et al., 2009). These data show that gay men and lesbian women cluster in families, but they do not say whether shared genes or environment are involved. Gay men and lesbian women cluster independently.

Comparing identical and fraternal twins suggests some genetic component. In one American study, 52% of identical male twins were both gay, while only 22% of fraternal twins were both gay (Bailey and Pillard, 1991). In a later study, 65% of identical male twins were both gay, and 29% of the fraternal twins were both gay (Whitam et al., 1993). Similarly, a study of woman reported that 48% of identical female twins were both lesbian, and only 6% of fraternal twins were both lesbian (Bailey et al., 1993). A British study of males and females combined showed that 25% of identical twins were both homosexual, whereas only 2.5% of fraternal twins were homosexual (King and McDonald, 1992).

These early studies invited twins to participate by placing advertisements in magazines and other sources likely to be seen by gay readers. More recent studies use a preexisting list of twins based on national censuses: Australia (Bailey et al., 2000), United States (Kendler, 2000), and Sweden (Långström et al., 2010). These also show that identical twins are about twice as likely both to be homosexual as fraternal twins. The chance that identical twins are both gay ranges from about 1/4 to 1/2, depending on the study, and is decidedly less than 100%. Thus, even though a genetic component may be present, environmental factors comprise 50−75% of the story.

Despite the aforementioned evidence for a small genetic component to homosexuality, contrary data also exist. The 1991 study already mentioned (Bailey and Pillard, 1991) also showed that an adopted brother of a gay man is twice as likely to be gay, 11%, compared with an adopted brother of a straight man, 5%. So, unless the adoptive parents are somehow selecting babies likely to become gay, something about the environment into which the adopted child is placed is contributing to sexual orientation as much as any genes are.

That homosexuality is to a large degree determined by environmental factors should not be taken as implying that homosexuality is reversible once it has been developmentally attained. Borrowing language from endocrinology, the environment may "organize" the development of behavior, or may "activate" already developed behavioral abilities. Organization is a permanent consequence from a stimulus, whereas activation reverses when the stimulus is removed. Many aspects of an individual's morphology are organized during development by environmental conditions. The resultant morphology is often quite adaptive, even though realized through environmental factors in addition to genetic factors. One may illustrate with an obvious botanical example. A vine of ivy produces small leaves in the sun and large leaves in the shade: these are the adaptive shapes for hot sunny spots and the moist understory, respectively. Once the leaf shape has been organized during development in a certain environment, the shape cannot be reversed, even if the environment changes. Similarly, homosexual capability may be organized to develop in certain social situations for which it is adaptive, and yet once attained, be impossible to reverse.

In addition to pedigree studies mentioned, geneticists have sought the location of the particular genes that contribute to homosexuality. The most famous of these is the study by Hamer and Pattatucci (Hamer et al., 1993, hereafter denoted as HP). HP defines homosexuality as a form of self-identity, irrespective of sexual practice. Hamer states, "As a geneticist, to be blunt about it, I don't really give a damn what label anyone uses, or even what they do, or with whom. I care about what they feel inside" (quoted in Burr, 1996, pp. 179−180). Similarly, Pattatucci states, "I want to know what's on your interior … do you feel that who you are now, your homosexual orientation, has always been part of you, part of who you are … even though your sexual behavior might have been with members of the opposite sex? … That's the important thing. The behavior is irrelevant compared to the core" (quoted in Burr, 1996, pp. 235−236).

HP made several points, some controversial:

1. HP confirmed yet again the tendency for Western gay men to cluster in families. The brother of a gay man had a 13.5% of being gay, whereas the brother of a straight man had only the baseline chance of being gay, which in this study was estimated at about 2%.
2. HP claimed that the distribution of men into the categories of straight and gay was nearly absolute: bisexuals were almost completely absent. The authors concluded, "it was appropriate to treat sexual orientation as a dimorphic rather than as a continuously variable trait."

This sorting into only two distinct categories is apparently an artifact of present-day social pressures within Western gay and straight communities. The subjects were self-acknowledged homosexual men recruited through the out-patient HIV clinics in the Washington DC area, and through local homophile organizations. Ninety percent of these men said they were nearly exclusively homosexual, and 90% of the straight men said they were nearly exclusively straight too, giving the impression of a clear-cut bi-modality. However, a present-day Western gay man cannot admit to being sexually interested in a woman any more than a present-day Western straight man can admit to being sexually interested in a man. HP did not solicit the organizations and magazines that offer safe space for those who do claim a bisexual identity. Moreover, in most cultures, same-sex sexuality is mixed with between-sex sexuality, implying that widespread bisexuality exits (Greenberg, 1988; Herdt, 1994).

3. HP provided demographic data on the life-history of gay men in the United States. The average age of first same-sex attraction was 10 years, 2 years before their average age of puberty at 12. The average age of self-acknowledgment was 15 years, and the average age of coming out was 21 years.
4. HP claimed that gayness in males is maternally inherited and linked to the X chromosome. The paper reports that maternal uncles and sons of maternal aunts (first cousins) of a gay man had a 7.5% chance of being gay, higher than the baseline chance of 2%. These purported genetic effects are small. Out of say, 100 maternal uncles and cousins of maternal aunts, only about seven are likely to be gay. Although seven is higher than the two who are likely to be gay on the paternal side, the claimed maternal genetic effect is very weak.
5. Building on the premise that some genetic component of gayness is maternally inherited, HP reported that a section on the X chromosome at the tip of its long arm called Xq28 was statistically related to gayness, a "gay gene." Out of 40 pairs of gay brothers, 33 shared the Xq28 section of chromosome X, and seven did not. This is an intermediate result. If something on Xq28 were absolutely needed to be gay, then all 40 brothers would share this chunk of DNA, whereas if only 20 brothers shared Xq28, then its random presence would indicate an irrelevance to gayness. The figure of 33 out of 40 is statistically significant, and HP concluded that some gene in the Xq28 region of the X chromosome tends to produce gayness in males. This claim is modest. Although a gene in the Xq28 region is claimed to have some effect, it is clearly neither necessary nor sufficient for gayness in males. HP repeated their study with similar, though somewhat weaker results (Hu et al., 1995).

The HP study was then repeated by a different group, in Canada, using the same overall design (Rice et al., 1999). Advertisements were placed in the Canadian gay news magazines for families in which there were at least two gay brothers. Forty-six families with two gay brothers and two families with three gay brothers were studied. The sexual orientation was confirmed for each subject by direct questions from a "gay interviewer," each subject read gay magazines, volunteered that he was gay, and his self-report was corroborated by interviewing the gay brother. These are behavioral criteria, not testimonials about one's "core identity." Considering the 46 brother-pairs, 23 would be expected to share Xq28 if this section were irrelevant to gayness, whereas all 46 would share their Xq28 if necessary for gayness in males. In fact, only 20 of the pairs shared their Xq28, a number low enough to show that Xq28 is irrelevant to whether a male becomes gay. So, there is no gay gene in the Xq28 region of the X chromosome. The Canadian investigators conclude, "It is unclear why our results are so discrepant from Hamer's original study … Nonetheless, our data do not support the presence of a gene of large effect influencing sexual orientation at position Xq28."

What then could account for the difference between Hamer et al., 1993 and Rice et al. (1999) concerning the gay gene supposedly on the X chromosome at position Xq28? The difference that jumps out is how people were as gay to begin with. The Canadian team did demand that a gay person affirm sexual orientation as a personal identity; sexual practice apparently sufficed, whereas HP insisted that the subject affirm their sexual orientation as a personal identity.

More recently, Mustanski et al. (2005) conducted a full-genome scan of sexual orientation in men by genotyping 456 individuals from 146 families with two or more gay brothers using microsatellite markers. These researchers also did not find evidence of any linkage between homosexuality and the X chromosome, but they did pick up traces of linkage to spots on the 7th, 8th, and 10th chromosomes, traces not strong enough to be statistically significant. A follow up by Ramagopalan et al. (2010) also did not find statistically significant evidence of linkage to male homosexuality, and the locations of what little linkage they did detect on chromosome 14 did not coincide with that found by Mustanski et al. (2005). The most recent study in this vein by Sanders et al. (2015) confirms a possible linkage to male homosexuality on chromosome 8 as Mustanski et al. (2005) reported but not on chromosome 14 as Ramagopalan et al. (2010) reported. In any case, linkage to autosomes, whichever is implicated, does not support maternal inheritance. However, Sanders et al. (2015) do claim a comparatively weak linkage to a region of chromosome X which might overlap Xq28. The linkage in all these studies is barely significant, if at all.

How to define homosexuality: whether it is sexual behavior, testimonial of personal identity, or some other criterion confounds genetic studies to this day. Some studies use solely behavior: "[our] survey included no direct question about self-defined sexual orientation. Actual partnered sexual behavior was assessed with two items: lifetime number of opposite-sex and same-sex individuals, respectively, that the respondent had ever 'been sexually together with'" (Långström et al., 2010). Others, like HP, are adamant that sense of personal identity should be the criterion for assessing homosexuality.

Even more recent studies are also failing to confirm a connection between homosexuality and maternal inheritance. Schwartz et al. (2010) report that although male homosexuals had more male homosexual relatives than heterosexual males did, these homosexual relatives were distributed approximately equally on both the maternal and paternal lines. They conclude their results "failed to support the importance of the maternal over the paternal line for male sexual orientation."

Some researchers prefer still another non-behavioral criterion for homosexuality called "psychological sexual orientation." A recent review asserts, "Whereas older studies tended to define sexual orientation behaviorally, most current researchers, ourselves included, define sexual orientation psychologically. Because sexual attraction and fantasy are less likely than behavior to be constrained by societal pressures, psychological sexual orientation is thought to be a more stable and fundamental trait" (Dawood et al., 2009). Despite the claim that "most current researchers" prefer their psychological criterion, the large population study of twins in Sweden just mentioned (Långström et al., 2010) does use solely a behavioral criterion, indicating that little consensus exists among geneticists even today on how to define homosexuality. This situation implies that any ensuing genetic analysis, however technically advanced, is of uncertain value.

It should be added that major difficulties attend any non-behavioral definition of homosexuality, such as any personal identity or psychological criteria just mentioned. The non-behavioral criteria do not involve characteristics that are exposed to natural selection. Natural selection evaluates results, not motivation. An evolutionary approach to homosexuality can address whether the expression of homosexuality is beneficial, not what motivates that expression.

In addition, the personal identity criterion is not applicable to explaining homosexual expression before the mid-1800s when homosexual identity emerged as a social category. Similarly, the psychological state of those expressing homosexuality in the past is largely unavailable, except perhaps as revealed in provocative gay publications from the Victorian era. Non-behavioral criteria are largely unworkable outside present-day Western settings.

Furthermore, an evolutionary account of homosexuality must address homosexuality not only cross-culturally and through history, but also across species. If homosexuality is defined in terms of personal identity, then no species we know of can be said to possess homosexuality, even though same-sex behavior might be common within it. Similarly, a psychological criterion is impossible to apply to other species, given that little is known (or even knowable) about the psychology of nonhuman animals. Using a non-behavioral criterion for homosexuality isolates its study from the wider community of biologists and reserves its investigation to medical researchers who are automatically pre-committed to a medical model that treats diversity as a pathology.

All in all, 30 years of genetic analysis have shown a possibly small genetic contribution to the development of homosexuality arising from unknown locations in the human genome. These 30 years have also revealed a large environmental contribution, much of which may act to organize the pathways of a person's organic development.

Gay Brains

For 30 years, neurobiologists have sought morphological differences between the brains of homosexual and heterosexual individuals. Much of this work has been motived by the so-called "neurohormonal theory" that posits that homosexuality is caused by unusual sex hormone levels prior to birth. In particular, male homosexuality is posited to depend on low prenatal androgen action and female homosexuality on high prenatal androgen action (Ellis and Ames, 1987). If sex hormone levels influence the development of homosexuality, they must be acting before birth rather than after birth because hormone treatments in adults have failed to influence sexual orientation, and no association has been found between adult hormone levels and sexual orientation (Byne and Parsons, 1993a,b). Focus therefore turns to hormones before birth rather than after birth.

The most famous studies claiming to support the neurohormonal theory pertain to what I have termed a tiny "rice grain of brain" within the hypothalamus called INAH-3. Allen et al. (1989) reported that INAH-3 is sexually dimorphic, being smaller in females than males. In a highly publicized article, LeVay (1991) confirmed that INAH-3 is sexually dimorphic, and in addition, reported that the size of INAH-3 in gay males was the same as in females. In heterosexual men, this rice grain of brain averages about 1/10 mm^3, in heterosexual women, about 1/20 mm^3, and in gay men, also about 1/20 mm^3. This study would appear to support the gay brain equals female brain theory, with male homosexuality presumably resulting from development under conditions of unusually low prenatal androgen concentration or with unusually weak androgen receptors.

But a follow-up by Byne et al. (2001) looked more carefully into the claims about INAH-3. They observed that the sexual dimorphism between heterosexual males and females pertains not only to the volume of the INAH-3 but also to the number of cells within that volume. Specifically, the volume of INAH-3 in HIV+ heterosexual males is about 0.11 mm^3 and in HIV+ females is about 0.07 mm^3, and the number of their neurons is about 1900 and 1100, respectively. Now compare the INAH-3 volume in HIV+ homosexual males: 0.10 mm^3, which is actually quite close to the HIV+ heterosexual male volume. In addition, the number of neurons in HIV+ homosexual males INAH-3 is 1800, a value not significantly different from that of HIV+ heterosexual males and quite different from that of females. In short, data simply do not support the claim that the male homosexual INAH-3 resembles the female INAH-3. Byne et al. (2001) conclude "We can neither ascribe any function to INAH-3, nor can we interpret the functional significance of its sexual dimorphism" and that, "sexual orientation cannot be reliably predicted on the basis of INAH-3 volume alone."

Well, if INAH-3 does not connote homosexuality, perhaps another part of the brain does. A small rice grain of nerve cells, a 0.25 mm^3 cluster, in the hypothalamus called VIP-SCN also shows sexual dimorphism. After about 10 years of age, males have about 2500 cells, and females about 1000 cells in this cluster (Swaab et al., 1994). VIP-SCN also seems to align with sexuality in males. You may be guessing that gay males have a female-sized VIP-SCN. Nope. Gay males have an even bigger VIP-SCN than straight males, which is in turn bigger than the VIP-SCN of females. So much for the belief that gay men have female brains (Swaab et al., 1995). Specifically, gay males had a volume of VIP-SCN that was 1.7 times as large, and with 2.1 times as many cells, as straight males. This result directly contradicts the neurohormonal hypothesis for male homosexuality. Homosexual and heterosexual male brains may indeed differ, but homosexual male brains do not differ by being anatomically more female-like than heterosexual male brains are.

Still, the neurohormonal theory for homosexuality just will not die. A review that actually cites the aforementioned studies (Mustanski et al., 2002) manages somehow to conclude, "Evidence consistent with the INAH-3 differences described by LeVay (1991) has been reported in one study (Byne et al., 2001), and these results are compatible with the neurohormonal theory." As just shown however, a close reading of the data in Byne et al. (2001) reveals that this study has been misquoted and that its findings are not compatible with LeVay (1991). It is time to throw in the towel on the neurohormonal theory for the development of male homosexuality.

That said, a postnatal, rather than prenatal, influence of hormones may be involved in differentiating gay and straight brains outside the hypothalamus. Cerebral maturation continues after puberty, especially in boys (Paus, 2005), providing a substrate for effects of social/environmental factors. Savic and Lindström (2008) have shown with PET and MRI scans that homosexual men align with heterosexual women and homosexual women with heterosexual men with regard to features of the cerebrum. Heterosexual men and homosexual women showed a rightward cerebral asymmetry as well as connections from the right amygdala.

Given enough research effort, differences in the brains of gay and straight males will surely accumulate. Consider though, what is the ordinary person-to-person variation in brain structure? Do the brains of politicians and poets also differ? Is some rice grain of Beethoven's brain shared by all composers? Is a different rice grain of Picasso's brain shared by all painters? Are there anatomical markers of ability in performing and graphic arts? Indeed, the part of the brain controlling left-hand fingers is larger in string players than everyone else (Elbert et al., 1995). Political orientation is correlated with brain structure (Kanai et al., 2011), as is musicianship (Bengtsson et al., 2005; Bermudez et al., 2009; Bermudez and Zatorre, 2005; Gaser and Schlaug, 2003; Zatorre et al., 2002) and also the ability to speak Chinese (Crinion et al., 2009). The difference between the brains of homosexual and heterosexual people is like the difference among the brains of any collection of people with diverse capabilities.

Transgender Brains

The inconclusive search for prenatal hormones influencing sexual orientation carried out during the 1990s and earlier have now given way during the 2000s and later to a search for prenatal hormones that organize the brain's development of gender identity. Here, the search for an influence of prenatal hormones is more plausible.

A divergence between genital sex and gender identity theoretically can emerge because an embryo's genitals sexually differentiate at a different time than its brain sexually differentiates (Swaab and Garcia-Falgueras, 2009; Bao and Swaab, 2011). Testosterone during the first 6–12 weeks of embryonic growth leads to the formation of male sexual organs, whereas a lack of testosterone during that period allows the genitals to develop as female sexual organs. In contrast, sexual differentiation of the brain occurs in the second half of pregnancy by the organizing effects of sexual hormones. Hence, the developmental of genitals and the brain are independent and chronologically separated by many months. Therefore, it is plausible to hypothesize that the genitals develop in one hormonal

regime and the brain in another, leading to a difference between genital structure and gender identity.

Indeed, many studies are now reporting that the physical brain structure of transgender people more closely resembles the sex they identify with rather than with their genital sex. This match of gender identity with brain sex rather than genital sex is now confirmed for the following: the number of neurons and volume of subcortical nuclei (Zhou et al., 1995; Garcia-Falgueras and Swaab, 2008), cerebral activation by visual erotic stimulai (Gizewski et al., 2009), functional alterations of regional cerebral blood flow (Nawata et al., 2010), and neuronal activation (Schoning et al., 2010), as well as structural differences of gray (Simon et al., 2013) and white matter microstructure (Rametti et al., 2011a, 2011b; Kranz et al., 2014). Saraswat et al. (2015) have contributed a recent review of evidence for a biological under-pining to gender identity. They review data on intersex people, neurohormonal data on brain structure such as that just noted, and also limited data on the genetics of steroid hormones that might be associated with transgender identity.

Moreover, depending on their sexual orientation, some transgender people show hypothalamus activation to odorous steroids intermediate between male and female controls (Berglund et al., 2008). In addition, the brain structure of trans women who are sexually attracted to women is explored with respect to white and gray matter, hemispheric asymmetry, and volumes of the hippocampus, thalamus, caudate, and putamen sections of the brain showing a complex pattern (Savic and Arver, 2011). Furthermore, the structural connectivity networks among different regions of the brains of transgender people differ from both non-transgender males and non-transgender females (Hahn et al., 2015). As before, it is again difficult to contextualize these technical details about brain structure among different people in light of the many differences in brain structure among people more generally.

Taking a synthetic view, I hypothesize that gender identity must develop in the first place as a prerequisite to the later developing of same-gender sexual orientation. I conjecture that gender identity has been attained at or near birth, whereas developing sexual orientation awaits experience during the first few years of infancy after birth (Roughgarden, 2004). This conjecture accords with anecdotes about how stable gender identity can be soon after birth (Colapinto, 2000), whereas the average age of realizing same-sex attraction is about 10 years after birth (Hamer et al., 1993).

But what exactly *is* "gender identity"? The brain structure studies do not answer this basic question. I have envisioned gender identity as a cognitive lens (Roughgarden, 2004). When a baby opens his or her eyes after birth and looks around, whom will the baby emulate and whom will he or she merely notice? Perhaps a male baby will emulate his father or other men, perhaps not, and a female baby her mother or other women, perhaps not. I imagine a lens exists in the brain that controls who to focus on as a "tutor." Transgender identity then is the acceptance of a tutor from the opposite sex. Degrees of transgender identity reflect different degrees of single-mindedness in the selection of the tutor's gender. Gender expression thus depends both on brain state—which is where the lens is, and on early postnatal experience—because the environment supplies the image photographed through that lens that is developed into brain circuitry. This hypothesis might be tested experimentally. In birds like canaries, males learn their song from male "tutors," often their fathers (Williams, 2008; Belzner et al., 2009). How does a male chick know to listen to his father instead of his mother? Female canaries sing a different song from males. I wonder if an occasional male chick learns his mother's song and an occasional female chick learns her father's song. Such gender-crossing birds would offer a model system to study jointly both transgender behavior and brain structure experimentally.

In summary, the brain structure of transgender people apparently does differ from non-transgender people because, in many details, their brains match the structure of the gender they identify with rather than the sex of their genitals. This presumably reflects the difference in timing of androgen action in early versus late embryonic growth, the different times at which the genitals and brain develop, respectively. In contrast, research shows no convincing evidence that the brain structure of homosexual people has been organized by the action of sex hormones prior to birth: the so-called neurohormonal theory of homosexuality is not true. The slight differences detected in the brain structure between homosexual and heterosexual people are well within the differences that distinguish all persons from one another reflecting their individual aptitudes and training. Thus, the developmental route to attaining transgender capability appears to involve a different androgen level at early verus late episodes prior to birth, whereas the developmental route to attaining homosexual capability is unknown but presumably involves experience during the first 10 years after birth.

Finally, I should alert the reader to the unfortunate language used by investigators of genetic correlates of sexual orientation. Their studies, carried out in medical schools and using pathologizing medical terminology, proceed with the unspoken assumption that homosexual capability is a deleterious trait. Their reports read like those tracing a genetic defect, such as hemophilia through a family pedigree. In fact, whether homosexual capability is deleterious or not is beyond the purview of genetic analysis and lies in the domain of human evolutionary biology, the discipline that considers a trait's function in its natural context.

Similarly, neurological studies of homosexuality and gender identity also convey the unspoken assumption that a heterosexual male/female binary is the normal biological condition for humans, in obvious contradiction with zoological and human cross-cultural data. Transgender people in particular are regularly described by medical researchers as possessing a neurobiological "intersex" condition because their brain structure matches their gender identity rather than their genitals. This terminology lumps transgender people with people possessing a so-called "disorder of sex development", for example, an unusual number of sex chromosomes or insensitive hormone receptors, which lead to genitals that pediatricians consider "too big" or "too small." This is not the place to debate the zoologically uninformed and clinically dubious procedures inflicted by the medical industrial complex upon babies born with unusual genital morphology. The point here is simple: all traits result from some developmental pathway, and all developmental pathways can be described with intimidating Latin- and Greek-derived technical terms. An innocuous trait like having ears big enough to attract the ridicule of a cartoon artist (like that of a recent American president) could be described as "macrotia," etymologically derived from "large" in Latin combined with "ear" in Greek. The condition of macrotia undoubtedly results from the action of certain genes, hormones, hormone receptors, etc., all of which could be spun as an intimidating story of developmental pathology. Of course, having large ears is not a pathology, and indeed, it might be especially advantageous in some circumstances. Similarly, if homosexual and transgender capabilities are evolutionarily advantageous, they will, of course, be realized through some biochemical pathway that features some particular timing of growth hormones during embryonic development. Describing that pathway with pejorative medical jargon does not affect whether the trait is in fact valuable and adaptive in its natural context.

The source of natural selection that promotes the evolution and development of homosexual and transgender capability lies in the function of these traits in the cultural contexts where they appear, the subject to which we now turn.

FUNCTION OF HOMOSEXUALITY

This major section of the chapter considers the functions of homosexuality and gender identity among humans in their natural cultural context. Theories for the evolution of homosexuality can be ordered along an axis that expresses an implicit value judgment as to homosexuality's worth. One may start at one extreme with theories that view homosexuality as completely deleterious, then move to theories that view homosexuality as deleterious in some circumstances and beneficial in others, then continue on to theories that view homosexuality as neutral and inconsequential, finally culminating at the other extreme with theories that view homosexuality as an adaptive trait mutually benefiting all participants. Subsections of this section present the major types of theories ordered along this deleterious-to-advantageous axis, and sub-subsections within these further describe important subtopics. In its entirety, this major section of the chapter presents a comprehensive look at all the varieties of theories presently available about why homosexuality and transgender identity have evolved.

Homosexuality Deleterious in All Circumstances: A Genetic Disease

This subsection pertains to theories for the evolution of homosexuality that assume homosexuality is unequivocally deleterious. The first sub-subsection considers the population-genetic relation between how common a genetically based trait is and how deleterious it is. The next sub-subsection presents a sample of theories that assume homosexuality is some type of pathology.

Criterion for a Genetic Disease

Until recently, researchers have taken for granted that homosexuality is a deleterious trait because it supposedly leads to lower reproduction by homosexuals compared with heterosexuals. Hence, researchers have traditionally looked for theories, often far-fetched, to explain how a deleterious trait can somehow become common through evolution.

To begin, we ask, is homosexuality in fact a genetic disease? Even if a gay gene does not exist, or if the influence of genetics on the development of homosexuality is limited and/or complicated, it is important to see what conditions must be satisfied before homosexuality could be considered a genetic disease. A genetic disease is a genetically determined condition that is deleterious at all times and under all conditions. Could homosexuality be considered a genetic disease?

Genetic diseases are automatically rare in the population because they are continually being weeded out by natural selection. The degree of rarity for a genetic disease is set by a balance between two rates: the rate at which the bad gene arises by mutation and the rate of elimination by natural selection. This level of rarity is called a mutation−selection equilibrium. A formula from population genetics expresses the connection among three numbers: how common a disease gene is, how deleterious it is, and how often it is regenerated by mutation from healthy genes.

Suppose, hypothetically, a population consists initially of straight individuals, and a mutation arises for same-sex attraction (a gay gene). Let the average net reproduction

by a straight individual be standardized to 1 and the average net reproduction of a gay individual be defined as 1-*s*. The *s* might be called the coefficient of deleteriousness. The bigger *s* is, the more deleterious it is to be gay. If *s* is 1, an average gay individual does not reproduce at all, which would be equivalent to reproductive sterility or lethality. If *s* is 0, an average gay individual reproduces just as much as an average straight individual, which would mean that being gay was not deleterious at all. An *s* between these extremes would indicate that an average gay individual does reproduce, but not as much as a straight individual does, so being gay is partially deleterious. The phrase "net reproduction" means that one takes account not only of how many offspring an individual produces (fecundity) but also the probability of living to reproductive age (survivorship). For example, if the number of offspring that an individual of reproductive age produces is 2, and if the chance of living long enough to reach reproductive age is ½, then the net reproduction by the individual is 1. ("Net reproduction" here is synonymous with what is usually called "Darwinian fitness" in the population-genetic literature.)

If the mutation rate producing a bad gene balances the rate that natural selection is eliminating the bad gene, then the frequency of births carrying the gay gene, *b*, works out to equal about *v*/*s*, where *v* is the mutation rate (for details see, eg, Roughgarden, 2004, pp 281−282, 446−447).

A typical mutation rate, *v*, is one in a million. So if gays do not reproduce at all ($s = 1$), they would be very rare, say around one in million, that is, each gay individual would be a new mutation. Indeed, almost-lethal traits like Huntington disease are present in frequencies of 5 per 100,000 births, hemophilia A at 1 birth per 8500, and so forth, very rare. Gay and transgender people are nowhere close to being this rare.

The formula relating *b* to *v*/*s* can be rearranged to predict how deleterious a trait must be given how common it is. Upon rearranging the formula, a trait's degree of deleteriousness, *s*, given how common it is, *b*, and the mutation rate, *v*, works out to be *v*/*b*.

According to 2011 demographic information on lesbian, gay, bisexual, and transgender people in the United States (Gates, 2011), 3.5% of adults in the United States explicitly identify as lesbian, gay, or bisexual (LGBT), and an estimated 0.3% of adults identify as transgender. Thus, approximately 9 million Americans identify as LGBT, a figure roughly equivalent to the population of New Jersey. Moreover, those who report *any* lifetime same-sex sexual behavior and/or *any* same-sex sexual attraction are substantially more common than those who explicitly identify as LGBT. Indeed, 8.2% report that they have at some point in their life engaged in same-sex sexual behavior, and 11% acknowledge at least some same-sex sexual attraction.

Let us use a nominal value of 1 in 20 (5%) as the frequency of gay people. How deleterious is it to be gay, given that gays are this common? Taking a mutation rate of 1 in a million divided by 0.05 yields a coefficient of deleteriousness, *s*, of only 0.00002. That is, the degree of overall deleteriousness for being gay must be infinitesimal.

Similarly, take a nominal value of 1 in 300 (0.3%) as the frequency of transgender people. How deleterious is it to be transgender? Taking the mutation rate of 1 in a million divided by 0.003 yields an *s* of 0.0003, which is also infinitesimal.

Although one can fiddle with the value of the mutation rate or use a more accurate formula to describe the mutation−selection equilibrium than the simple heuristic of $b \approx v/s$, the conclusion is inescapable that gay and transgender people are 10,000 times more common than would be consistent with assuming that being gay or transgender express a trait deleterious under all conditions.

Candidate Genetic Diseases

That said, researchers have conjured no shortage of theories that cast homosexuality as a pathology. Blanchard has been especially energetic in this effort (Jannini et al., 2010; Blanchard and Klassen, 1997; Blanchard, 2008), proposing that homosexual men who have older brothers owe their homosexuality to an autoimmune disease acquired from their mother. The rationale for this suggestion comes from the so-called "birth order effect" among gay men.

Blanchard and Bogaert (1996) calculated that each additional older brother increases a male's odds of homosexuality by 33%. Bogaert (2006) found that biological brothers increase the odds of homosexuality in later-born males, even if they were reared in different households, whereas stepbrothers or adoptive brothers have no effect on sexual orientation. This suggests that the birth order effect is caused somehow by prenatal conditions.

To explain the birth order effect, Blanchard and Bogaert (1996) formulated what they call the maternal immune hypothesis. According to this hypothesis, cell or cell fragments from a male fetus enter the maternal circulation during childbirth. The mother's immune system recognizes these male substances as foreign and starts producing antibodies against them. The mother's antibodies then cross the placenta into a subsequent male fetus. When absorbed by the male fetus, these antibodies somehow influence the sexual differentiation of the fetal male brain in a female direction so that the individual will later be attracted to men rather than women. Blanchard acknowledges, however, that because half or more of all homosexual men have no older brothers, other causes must account for at least half of existing homosexual men.

Two problems arise in the autoimmune disease theory of male homosexuality. First, as we have seen, brains of male

homosexuals do not resemble the brains of females regardless of whether that resemblance is supposed to have been caused by prenatal hormones or by prenatal antibodies.

Second, the autoimmune theory of male homosexuality is a developmental theory, not an evolutionary theory. Evolutionarily, it does not matter *how* the birth order effect is produced, what matters is what the advantage is for more younger brothers to be homosexual than older brothers. The autoimmune theory of homosexuality does not address the evolution of homosexuality. It merely casts the development of homosexuality in pathological sounding language. And the theory is incomplete because the connection between maternal antibodies to a male fetus and the brain structure of subsequent male offspring is left dangling mysteriously.

Other disease theories for the development of human homosexuality are regularly given by researchers to the news media. A scientist who declined to be quoted by name stated to the science writer, Chandler Burr, that homosexuality was caused by a mitochondrial gene or a bacterium transmitted exclusively through females. He went on to brag, "homosexuality may be a type of bacterial infection we've just never encountered before, one that we may eventually be able to eradicate with an antibiotic" (Burr, 1996, pp. 257–259).

These homosexuality-as-a-disease theories all spring from an uncritical acceptance of homosexuality as universally deleterious. If one accepts that premise, one is forced to conjure up scenarios whereby a deleterious trait can become as common as homosexuality is. The widespread uncritical acceptance of homosexuality as deleterious by the medical community explains why so many foolish disease theories of homosexuality keep popping up.

Homosexuality Deleterious in Some Circumstances and Beneficial in Others

This subsection pertains to theories for the evolution of homosexuality that assume homosexuality is deleterious in some circumstances and beneficial in others, or has positive consequences in addition to negative consequences. The first sub-subsection considers what the cost is to being homosexual in terms of lower fertility. The next two sub-subsections present two different theories for how homosexuality may offer other, possibly indirect, fertility benefits that may compensate for its fertility cost.

Fertility Cost of Homosexuality

If not always deleterious, perhaps homosexuality is somehow occasionally beneficial, directly or indirectly. This contingent benefit might offset some of its presumed deleteriousness and account for homosexuality being much more common than it would be if it were simply a genetic disease.

Direct evidence is surprisingly scanty as to how deleterious homosexuality actually is for fertility, setting aside for the moment the impact of homosexuality on survival.

For lesbian women, a 1988 US survey reported that the mean number of children born to women with homosexual experience was 1.2 compared to a mean of 2.2 for women without homosexual experience (Essock-Vitale and McGuire, 1988). A 1994 survey reported that 67% of lesbian women were mothers, compared with 72% for straight women (Yankelovich Partners, 1994). A 1995 study of contemporary British women showed bisexual women have a higher fecundity to age 25 and no significant difference in lifetime fecundity compared to heterosexual women (Baker and Bellis, 1995). Thus, lesbian and bisexual woman apparently have about the same or higher reproduction than straight women.

For gay men, the 1994 study showed that 27% were fathers, compared with 60% for straight men (Yankelovich Partners, 1994). Of 655 homosexual and bisexual men in contemporary Japan, 83% have offspring (Isomura and Mizogami, 1992). A 1997 investigation surveyed 256 homosexual men in Australia who were older than 49 years of age. Of these about 63% were or had been married and about 56% had children (Van de Ven et al., 1997). Clearly, gay men are not reproductively sterile.

However, King et al. (2005) asked male attendees at two central London clinics for sexually transmitted infections to complete anonymous questionnaires. They compared offspring production from 403 white gay males with 301 white straight males. But the study excluded bisexual men. Not surprisingly, they found that gay males in this sample of people on the average produced only 0.002 offspring, whereas the straight men produced 0.36 offspring.

Schwartz et al. (2010) recruited a sample of 894 straight males and 694 gay males from 16 gay-themed festivals and eight general community festivals in the United States and Canada. Gay males produced on the average about 0.2 offspring and straight males about 0.6.

Clearly, no one really knows what the impact of homosexuality on fertility is. It is difficult to obtain a representative sample of people. Those still in the closet and those who are bisexual are not as likely to turn up at gay pride events or AIDS clinics as those who are out and sexually active in the gay community (cf. Gates, 2012). This will lead to an underestimate of the fertility of homosexual people.

Furthermore, the fertility cost of homosexuality clearly depends on the culture in with the behavior takes place. An

extreme example comes from Melanesia where homosexual behavior is well known. About 10–20% of Melanesian societies require *all* men to participate in homosexual as well as heterosexual sex (reviewed in Herdt, 1994). Obviously homosexual behavior there not only involves no cost, but to the contrary, failure to share in homosexual behavior is deleterious.

Studies that deliberately omit bisexual people from their survey samples commit a particularly serious mistake with regard to the evolution of homosexuality. Hypothetically, if exclusive homosexuality represents a genotype homozygous for a gay gene, bisexuality a genotype heterozygous with both the gay gene and a straight gene, and exclusive heterosexuality a genotype homozygous for the straight gene, then the course of evolution of homosexuality, and whether a polymorphism exists, depends on knowing the average net reproduction by all three genotypes of individuals, not only two of the types. Similarly, for more complex genetic mechanisms, the net reproduction for all the genotypes associated with any particular genetic mechanism must be known if the course of evolution based on that mechanism is to be predicted.

Moreover, Western national surveys of LGBT people consistently and clearly show that bisexual people are about as common as gay and lesbian people (Gates, 2011), contrary to the presumption often expressed by gay researchers that bisexuals are rare (eg, Hamer et al., 1993). What is going on is that bisexual people are not socially organized around their sexuality to the extent that gay people are, so survey protocols that sample primarily gay venues amplify the gay component of the LGBT population while underestimating the bisexual component.

What then, if anything, can be said about the impact of homosexuality on fertility? In the Western cultures that have been sampled, it seems fair to summarize that homosexuality in males might involve a reduction of say, 50%, in fertility relative to heterosexuality.

To explain homosexuality's evolution, a 50% reduction in fertility would need to be compensated somehow by a doubling of the probability of survival if the net reproduction of homosexuals is to match that of heterosexuals. Today's society in many countries is certainly not kind to the survival and health of gay and lesbian people (eg, Dean et al., 2000), but the matter may have been entirely different during human evolutionary history. The possibility that homosexuality may increase *survival* through building alliances and partnerships, and thereby compensate for the fertility cost of homosexuality, is taken up in detail later in "Homosexuality Promotes Alliances and Partnerships". Here, the next sub-subsections focus on possible *fertility* benefits that might compensate for the fertility cost of homosexuality.

Fertility Benefit of Homosexuality: Sex-Antagonistic Pleiotropy

Although the fertility cost of homosexuality may be compensated by increased survival, other possible avenues for compensation exist too. One idea receiving current attention is that the gay gene functions to increase *any* individual's sexual attraction to men. The gene is supposed to cause females to seek heterosexual mating more than females lacking the gene, yielding more offspring. As a side effect, the gene is also supposed to lead males to seek more homosexual mating than males lacking the gene, yielding fewer offspring. Thus the gene is beneficial in females and deleterious in males. This genetic mechanism for evolution is called sex-antagonistic pleiotropy.

The theoretical possibility of sex-antagonistic pleiotropy accounting for male homosexuality has been explored using mathematical models by Gavrilets and Rice (2006) and Camperio Ciani et al. (2008). The applicability of this mechanism to humans has been proposed by Camperio Ciani and colleagues in a series of papers (Camperio Ciani et al., 2004, 2009; Iemmola and Camperio Ciani, 2009) and in *Drosophila* by Hoskins et al. (2015).

In a sample of homosexual and heterosexual people drawn from Northern Italy, Camperio Ciani et al. (2004) found that the mothers of male homosexuals had on the average about 2.7 offspring, whereas the mothers of heterosexual males had on the average about 2.3 offspring. Camperio Ciani et al. (2009) extended their samples to include bisexual men. Here, they found that the mothers of homosexual men had on the average 2.6 offspring, the mothers of bisexual men had on the average 2.7 offspring, whereas the mothers of heterosexual men had on the average 2.1 offspring. These results are consistent with the hypothesis that homosexuality results from genes that promote a general sexual attraction to males by any individual regardless of sex.

Camperio Ciani et al. (2008) found in their mathematical models that the enhanced male sexual attraction trait required a certain minimal genetic system: the genetics for the trait must consist at least of two loci with two alleles at each locus, and at least one of the loci must be located on the X chromosome. If the trait was determined by a single locus, either autosomal or X-linked, or by two loci neither of which is on the X chromosome, then the predicted evolutionary process would not agree with their data.

Four objections might be raised to this sex-antagonistic pleiotropy hypothesis for humans. First, the size of the difference between the fecundity of mothers of homosexual males and mothers of heterosexual males is not very big. An increase of only 0.5 extra offspring produced by mothers of homosexual males may not be enough to compensate for the 50% loss of fertility in her homosexual children.

Second, although Camperio Ciani's et al.'s (2004) data showed evidence of maternally inherited genetic factors favoring male homosexuality, other studies do not. Schwartz et al. (2010) are explicit: "none of our findings supported the hypothesis that maternal inheritance of male sexual orientation was a more significant factor than paternal inheritance." They go on to say, "the lack of elevated 'transmission' of male sexual orientation in the maternal line in the current study supports the notion that hereditary contributions to male sexual orientation do not predominantly reside on the X chromosome, but instead primarily reside elsewhere, that is, on the autosomes." Recall, too, this chapter's previous discussion concerning Hamer et al.'s (1993) study claiming a gay gene is on the X chromosome. That study has not been confirmed, and Mustanski et al.'s (2005) whole-genome scan and others found little or no evidence of genes for homosexuality on the X chromosome, or elsewhere for that matter. Thus, Camperio Ciani's findings about maternal inheritance of homosexuality are apparently not general, undercutting their requirement for a gay gene on the X chromosome.

Third, no direct information about behavior itself is available. Do mothers of homosexual children actually show an elevated sexual attraction to men compared with mothers of heterosexual children? Camperio Ciani and colleagues do not survey any of the women implicated in their hypothesis, only men. So far as the women are concerned, we must content ourselves solely with statistics on their "fecundity." No one actually asks the women themselves to see whether those with more homosexual children are in fact more attracted to sex with men than the mothers of solely heterosexual children. On reflection, mothers of a gay child may have more children than mothers without any gay children for many reasons having nothing to do with an elevated sexual attraction to men. The mother of a gay child may have an additional child to have grandchildren. Or the social dynamics within large families might promote situations where being homosexual is adaptive.

Fourth, resting an explanation for a trait as widespread as homosexuality on the peculiar properties of a specific genetic mechanism is dubious theoretically. If an increase in the degree of sexual attraction by females to males is adaptive, natural selection need not shackle this trait to a deleterious trait in males. Beyond the two primary loci for elevated sexual attraction to males in the Camperio Ciani et al. (2008) model, a third locus might be introduced, a modifier locus (eg, Feldman, 1972), whose alleles alter the extent to which the primary genes are expressed in males. Modifier genes will then increase to reduce any deleterious impact in males of a trait that is beneficial in females. The genetic mechanism that Camperio Ciani et al. (2008) relies upon is not structurally stable to an increase of genes that would alter the genetic system itself, removing the peculiar properties that enable male homosexuality to be interpreted as a deleterious side effect of a gene that is beneficial to females.

Fertility Benefit of Transgender: Helpers at the Nest

Another way to compensate for the fertility cost of homosexuality is for the gene to increase the fertility of relatives. If a homosexual person augments the fertility of a close relative, the person theoretically can compensate for their own fertility cost by propagating the genes contained in the offspring of their close relatives. This hypothesis is a version of what evolutionists term kin selection.

By this theory, gays and lesbians are similar to avian helpers at the nest, offspring who stay around their nuclear family to help in raising brothers, sisters, and cousins who then go on to do the reproducing (Wilson, 1975, 1979). When initially proposed, this theory broke new ground by valuing the contributions to family and society that gay and lesbian people might potentially make and was a step forward in de-pathologizing same-sex sexuality. However, a limitation of this theory to begin with is that it does not explain why helpers who remain as part of an extended family would specifically be gay or lesbian.

Important though this suggestion has been historically, helping at the nest does not appear to hold the answer to why homosexuality has evolved in humans. In a 2001 study (Bobrow and Bailey, 2001), 66 homosexual and 57 heterosexual men were recruited using advertisements in free urban alternative and gay publications. The name of the city is not mentioned, but it is presumably Chicago because that is where the investigators were located. Based on questionnaires, homosexual men were no more likely than heterosexual men to channel resources toward family members. To the contrary, heterosexual men tended to give more financial resources to siblings than homosexual men. Furthermore, homosexual men were somewhat more estranged from family members, especially from fathers and oldest siblings than heterosexual men.

A follow-up study in 2005 (Rahman and Hull, 2005) found similar results based on 60 homosexual and 60 heterosexual men recruited from East London and Essex. Questionnaires revealed no significant differences between heterosexual and homosexual men in general familial affinity, generous feelings (willingness to provide financial and emotional resources), and benevolent tendencies (such as willingness to baby-sit).

In contrast to the studies from urban Western settings, evidence supporting kin selection theory does come from transgender people in Samoa.

Like other Polynesian cultures, Samoan culture features a third gender for male-to-female transgender people, called the fa'afafine (pronounced, fah-ah-fah-fee-nay).

They often are "strikingly feminine" and can easily pass as women in public by wearing make-up, jewelry, women's clothing, feminine hairstyles, and speaking with a feminine voice, and moving in a feminine manner (Bartlett and Vasey, 2006). As Schmidt (2003) explains, drawing on her own field work and that of Poasa (1992) and Besnier (1994), parents identify fa'afafine when they are children because of a propensity for feminine tasks. Families do not equate this early preference for feminine labor with sexual orientation. Upon reaching adulthood, sexual relations with men are seen as a consequence of being fa'afafine rather than as a defining criterion for inclusion in the category. Fa'afafine have traditionally been, and generally still are, identified by their labor preferences not sexual preferences. Furthermore, fa'afafine do not identify as gay because this is interpreted as indicating a straight man having sex with another straight man. Thus, sexual relations between fa'afafine and straight men would be described as homosexual and heterogenderal. This fact means that evidence of kin selection found for fa'afafine pertains primarily to the evolution of transgender expression: any implications for the evolution of homosexuality are incidental.

In Samoa, child-care activity is largely a feminine gender role activity (Vasey and VanderLaan, 2009). When their children are infants, Samoan mothers take primary responsibility for child care. New mothers are surrounded by kinswomen who take care of her other children while she rests and recovers. Infants are often handed over for extended periods of time to the care of an older female relative, usually a sister or a cousin. Some women offer specialized child-care activities, such as massaging infants and small children to cure muscular soreness. Grandmothers often feed children if mothers are away. In addition, aunts and grandmothers often instruct young girls in handicrafts and other work.

Vasey et al. (2007) gave questionnaires to 38 self-identified fa'afafine and 43 self-identified straight men in Independent Samoa. Vasey et al. (2007) found that the fa'afafine and straight men did not differ in their overall generosity and allocation of financial resources toward kin, nor did they differ in general neediness or financial resources obtained from kin. However, fa'afafine did carry out a suite of activities pertaining to their family's child care more than the straight men did: babysitting for an evening, babysitting on a regular basis, taking care of the children for a week while their parents are away, buying toys for the children, tutoring the children, helping to expose the children to art and music, contributing money for day care, contributing money for the children's medical expenses, and contributing money for the children's education. A follow-up study (Vasey and VanderLaan, 2009) supplied questionnaires to 136 self-identified fa'afafine, 182 self-identified straight men, 40 women without children, and 89 mothers. In this study the fa'afafine had the highest willingness to carry out the suite of child-care activities, higher even than the mothers, the women without children and the straight men in the sample.

Readers who refer back to the papers by Vasey and colleagues may be confused by the terminology used. Vasey describes the child-care activities by the fa'afafine as "avuncular," a word that means uncle-like even though the activities themselves are exactly the same as those used by women while carrying out their child-care responsibilities. The activities might better be described by the word, "materteral" which means aunt-like because the fa'afafine are performing in a feminine work role in accordance with why they identify as fa'afafine to begin with. By focusing on the biological sex of the fa'afafine rather than their gender expression, Vasey is considering them as uncle-like even though their behavior is aunt-like, erasing their gender identity in favor of a sexual identity.

There is a backstory to Vasey's gender identity: erasing language. Vasey subscribes to a controversial typology of transgendered people introduced by Blanchard (1989). By this typology, all transgender women belong to two distinct non-overlapping classes: heterosexual cross-dressing men (CD-trans) and homosexual men (H-trans). Blanchard envisions that CD-trans women are heterosexual men pursuing a cross-dressing sexual fetish to the extreme of having a vagina surgically constructed in them. He envisions that the H-trans women are homosexual men seeking to improve their attractiveness for sex with men. In the Blanchard typology, bisexuals do not exist; they are homosexuals in self-denial. In addition, gender identity does not exist; transsexual claims to identifying with the gender opposite to their sex are delusions.

Research from the Blanchard perspective comes primarily from faculty at three institutions: The Clarke Institute of Psychiatry in Toronto (now absorbed into the Center for Addiction and Mental Health), the psychology department of Northwestern University, and more recently the psychology department in the University of Lethbridge. Vasey is from Lethbridge.

The Blanchard typology ignited 20 years of vitriolic controversy, largely because of its proponent's incendiary animus toward transgender people. (For a history of the disputes, see http://ai.eecs.umich.edu/people/conway/conway.html and http://www.tsroadmap.com/info/bailey-blanchard-lawrence.html). The Blanchard typology is increasingly discredited among academics (Moser, 2010; Nuttbrock et al., 2011; see also Smith et al., 2005). Hence, the interpretation favored in this paper is that transgender expression does exist as a primary trait, and not as the derivative of some sexual drive. Therefore, the evidence for kin selection among the Samoan fa'afafine is regarded as pertaining to the evolution of transgender expression, not to the evolution of homosexuality. The sexual orientation of the fa'afafine is taken to be a

by-product of the fa'afafine's social expectations, consistent with the ethnographic studies on Samoa.

The case for kin selection favoring the evolution of transgender expression among the fa'afafine has not yet been made quantitatively. Although the contribution of the fa'afafine to child care undoubtedly increases the reproduction from their families, as evidenced by the larger family sizes of families with fa'afafine compared to families without, it is not clear if this effect is large enough to fully compensate for the fertility cost of the homosexuality that the fa'afafine practice.

The generality of a kin selection theory for the evolution of transgender expression as in the fa'afafine is not clear. The hijra in India, for example, are generally cast out from their extended families and instead join collectives managed by a hijra guru (Nanda, 1999). On the other hand, transgender people, such as the two-spirited women of some Native American nations do participate to some extent in women's labor roles but also have unique social roles, such as mediating disputes between men and women and acting as shamans (Herdt, 1994; Roscoe, 1991, 1998).

Although the importance of fa'afafine child care has been discussed in the literature with regard to kin selection, reflecting the early formulation originating with Wilson (1975), a contemporary quantitative analysis of the fa'afafine contribution to reproduction might best be framed in terms of family selection, or multilevel selection (Wilson and Wilson, 2007). Indeed, the social roles of third-gender people that go beyond helping in child care, and extend to mediating disputes and to leading religious ceremonies that bind people together, might produce tribes that prosper more than tribes lacking such social glue. Differential success of tribes with and without third-gender people might form the basis for a multilevel selection theory for the evolution of transgender expression. Such transgender expression might include homosexuality as a side effect. The sex in such situations would be homosexual and heterogenderal.

A theory emphasizing the value of helping in child care and thereby increasing family size needs to explain why such care is offered specifically by transgender people. Why could not anyone else provide the help, say other women, or the men: why a transgender woman specifically?

As a possible answer, I first conjecture that the gender role whereby child care is primarily the women's responsibility is an ancient and preexisting condition. Next, suppose an increase in size of the female labor pool is favored through multilevel selection on families, despite the constraint of an underlying 50:50 biological male-to-female sex ratio. In this situation, evolution can add to the female labor pool by tuning the amount and timing of the delivery of prenatal hormones to produce a female-identifying individuals from within the male pool. This allows the production of more people carrying out female labor tasks rather than male tasks despite the population biological sex ratio remaining fixed at 50:50. That is, the phenotypic male-to-female sex ratio is free to vary even though the biological sex ratio remains 50:50.

Homosexuality Selectively Neutral

This subsection pertains to theories for the evolution of homosexuality that assume it is costless, a harmless by-product of other activities that are adaptive. A sub-subsection presents a well-known case with Japanese macaques and another sub-subsection presents the population-genetic criterion for a trait to be neutral with respect to natural selection.

Japanese Macaques

This harmless by-product view of homosexuality, first stated most clearly by Futuyma and Risch (1984), has been further developed and applied to the case of female homosexuality in Japanese macaques (Vasey, 1998). After reviewing and dismissing possible functions of homosexuality in female Japanese macaques, Vasey concludes the females carry out homosexuality for its sheer pleasure. He writes, although "sexual pleasure was selected for because it motivates individuals to engage in fertile sex … sexual pleasure is not specific to reproductive sex but can be satisfied by many non-reproductive sexual outlets as well."

All Japanese macaque females participate in what are called female–female consorts. These are short-term relationships (STRs) that last for less than an hour up to four days. During this time, the two females mount each other frequently with genital–genital contact. When not having sex together, they huddle, sleep, and forage together, groom each other, and defend each other from challenges. For the duration of their STR, a pair is monogamous. After a few days though, they re-assort and form new STR's with one another.

Female Japanese macaque back each other up while together in an STR. The lower ranking member of an STR increases in rank temporarily because of her partner's support (Vasey, 1996). This temporary increase in rank ends when the STR dissolves. The mountings are bidirectional and mutually pleasurable, and they show no sign of a dominance or submissiveness within the relationship (Vasey et al., 1998).

According to the theory that homosexuality is selectively neutral, homosexuality does not disappear during evolution because homosexuality is harmless. Female macaques have lots of offspring, and they do participate in heterosexual mating whenever they need some sperm. Homosexuality does not apparently interfere with their reproduction, so how could natural selection remove this harmless behavior?

Thus, by chance, according to the selective neutrality theory, homosexuality has drifted over the course of evolution into prominence in some species, while remaining nearly absent in others. Or, in some species, chance has genetically linked homosexuality to certain important genes and homosexuality has "hitchhiked" into prominence on the coattails of those genes. Homosexuality is viewed as beneath natural selection's radar screen and subject only to the winds of passion.

Do Japanese macaques have lots of free time to hang around? Is every day another day in paradise, an endless party filled with evolutionarily meaningless play? Why should macaques be so lucky, while the rest of us poor sods have to work for a living? Actually, homosexual interaction would seem to occupy far too much time in the lives of female macaques to be evolutionarily incidental. So, is homosexuality plausibly a selectively neutral trait?

Criterion for Selective Neutrality

Evolutionary theory offers quantitative rule of thumb for whether homosexuality can be a selectively neutral trait. If the strength of natural selection against the trait as measured by s, the coefficient of deleteriousness, is less than the reciprocal of the population size, then the trait is neutral; it cannot be touched by natural selection. Conversely, if s is greater than the reciprocal of the population size, the trait is deleterious and will tend to be removed by natural selection resulting in a selection/mutation equilibrium, as previously discussed.

If s is less than the reciprocal of the population size, indicating that the gene for homosexuality is neutral, then the strength of genetic drift, the ever-present random fluctuation of gene pool frequencies, exceeds the strength of the natural selection against the gene. That is, if homosexuality is selectively neutral, any small "signal" of natural selection is buried in the ever-present "noise" of the gene pool's random fluctuations.

For example, if the population size of Japanese macaques is 50, the reciprocal of the population size is 1/50, or 0.02. Suppose the average net number of offspring left by non-homosexual females is scaled to 1.0, and the average net number of offspring left by homosexual females is 0.99. Then s, the coefficient of deleteriousness, is 0.01. In this case, homosexuality is selectively neutral. However, if the homosexual females have even a little bit fewer offspring than the homosexual females because of wasting time in homosexual mounting, say homosexual females leave 0.95 offspring to every one left by a non-homosexual female, then s is 0.05, which is greater than the reciprocal of the population size. In this case, homosexuality would not be neutral and would evolve to be present at low frequency in a mutation/selection equilibrium. Thus, for homosexuality to be evolutionarily neutral, females who do, and who do not, participate in short-term homosexual relationships need to have an almost exactly identical average life-long net reproduction, which seems highly improbable.

Vasey (in comment following Kirkpatrick, 2000) reiterates his belief that human homosexual behavior is a neutral by-product of direct selection for heterosexual sexual pleasure, that homosexuality is expressed solely for sexual gratification. As such, Vasey claims that homosexual behavior has no evolutionary function and simply will not be selected against, presuming it does not interfere with the participants' heterosexual efforts. Vasey allows, however, that homosexual behavior could be co-opted to serve a sociosexual role, such as alliance formation (an exaptation). As such, Vasey envisions that homosexuality may then come under positive selection because of its beneficial effects on fitness. The problem with this seemingly appealing theory is that the initial condition is improbable. That is, selectively neutral traits do not patiently await, so to speak, to be pressed into duty for some adaptive function. A time-consuming behavior like homosexuality as practiced in the Japanese macaques would almost surely not have been neutral to begin with. Instead, if homosexuality has evolved as an offshoot from heterosexuality, then it will have been advantageous immediately without passing through an intermediate state of selective neutrality awaiting to be adaptively rescued.

To the contrary, homosexuality in Japanese macaques is apparently beneficial now and always has been. Indeed, all females do participate in homosexual STRs. If there is a benefit to homosexuality, the coefficient of deleterious, s, is negative. The reason why homosexuality might be beneficial in Japanese macaques is that the fate of a female who decides not to participate in homosexual STRs would seem bleak because she is likely to be kicked out of the group and left to die soon thereafter. If participating in STRs is necessary for inclusion in female social groups, then those who are not homosexual would be at a selective disadvantage. In this species female same-sex sexuality is what I am calling a social-inclusionary trait (Roughgarden, 2004).

Homosexuality Selectively Advantageous

This subsection pertains to theories for the evolution of homosexuality that assume homosexuality is a positive adaptation for its participants. For these theories, the commonness of homosexuality is no problem whatsoever. Indeed, the problem with these theories is to explain why everyone is not homosexual. Two sub-subsections offer different types of theories for why homosexuality is adaptive.

Homosexuality Promotes Alliances and Partnerships

Two papers in 2000 advance the hypothesis that homosexual behavior is advantageous by promoting bonding in varying circumstances.

Greenberg (1988) classifies homosexual behavior into three types. One is transgenderal exemplified by the fa'afafine, hijra, and so forth, as previously discussed in "Fertility Benefit of Transgender: Helpers at the Nest". That is what I term homosexual and heterogenderal. Instead, this section focuses on homosexuality that is both homosexual *and* homogenderal. In this regard, Greenberg distinguishes two types: adult-peer (which he calls egalitarian) and the patron/client (which he calls transgenerational). Adult-peer homosexuality is type most common in contemporary discourse about gay marriage; both partners are nearly the same age, and they belong to the same generation. However, patron/client homosexuality is evidently the most common type of homosexuality cross-culturally and throughout history.

Muscarella (2000) focuses on the value of homosexual behavior in male patron/client relationships which he states, "has been a persistent feature of the human species since recorded history." Continuing, Muscarella (2000) writes, "The long history of institutionalized homosexuality between higher status and lower status males," usually of different ages by five years or more, produces "relationships [that] tend to socialize the youths into the adult male role, nurture and protect the youths and provide the basis for life-long friendships, social alliances and social status … Social status, a reflection of political strength and alliances, appears to have played a large role in the evolutionary history of human male reproductive success."

For women, Muscarella (2000) suggests that homosexuality provides bonds of friendship that lead to mutual assistance in raising children, assuming paternal assistance is absent in primitive societies. Here too, homosexuality is hypothesized to provide higher reproductive success.

These conjectures about how homosexuality evolved feedback to determining the type of environment in which homosexuality develops during infancy. Muscarella (2000) writes, "Homoerotic behavior may be evoked as a normal response to placement in an environment which closely resembles the environment in which it evolved and was adaptive in the evolutionary past."

Kirkpatrick (2000) generalizes the discussion about homosexuality leading to alliances beyond a focus on the patron/client. He writes, "If homosexual behavior also serves non-conceptive functions, such as the maintenance of same-sex alliances (long-term supportive relationships) that aid in resource competition or in cooperative defense, then homosexual behavior will be under positive selection … Homosexual behavior is a *survival* strategy, not a *reproductive* strategy."

Kirkpatrick (2000) mentions many examples. I have condensed his account as follows: "Pair-bonds between adult-peer males in many societies of native North America reduced variance in food intake and provided for cooperative defense. Males become companions in hunting, in war, and in fortune and have a right to food and lodging in each other's cabin. Within patron/client same-sex alliances in Melanesia, the younger client provides labor in the fields (and sexual services) while the older patron provides food and education. In precolonial Tahiti and Hawaii, the clients of powerful patrons gained prestige, as did clients in classical Athens and 15th-century Florence. In ancient Crete, men without same-sex sexual partners were at a social disadvantage. Same-sex sexual partners of the Japanese samurai gained both martial training and land. In classical Athens and in Tokugawa Japan, same-sex alliances were thought to be more dangerous to entrenched interests than female-male alliances. And lest one think of homosexual and heterosexual relationships as antagonistic, both female-exchange marriage and homosexual behavior integrate with each other in Melanesia to link individuals in complex chains of mutual dependency and obligation. Among the Etoro, a patron's ideal client is his wife's younger brother, effectively linking wife and client in a hetero/homosexual threesome marriage in which one co-spouse is reproductively active."

Tantalizing clues also exist that homosexual behavior becomes expressed more in complex rather than simple societies. Homosexual behavior occurs more often in agricultural than in hunter-gather societies, and more often in larger social groups (Barber, 1998). Homosexual behavior may also be more frequent when political networks rather than independent individuals are empowered, and it may be expressed more in industrial nations after their demographic transition, that is, the shift in a population's demography from high reproduction to high survival following industrialization (Dickemann, 1993).

A difficulty faced by a theory of homosexuality as a form of alliance building is that male−male alliances can be built without using sexuality. This brings me to my own contributions pertaining to the evolution of homosexuality (Roughgarden, 2012a).

Physical Intimacy Promotes Cooperative Coordination

My hypothesis is that it is specifically the physical intimacy in homosexuality that is important, not sex. I conjecture that the research focus on the sexual aspect of homosexuality merely reflects our fetishizing of sex and not what is important about homosexuality.

Instead, I hypothesize that genital–genital contact is a special case of physical intimacy that pertains uniquely to mammals who happen to have genitals filled with pleasure sensing neurons and who happen to use their genitals for signaling and social purposes other than the exchange of gametes in heterosexual mating. Indeed, I hypothesize that mutual grooming in mammals, mutual preening in birds, even calling together in chorus, also fulfill a similar function to the physical intimacy of homosexuality.

And what function is that? The reciprocal exchange of pleasure in these behaviors provides coordination to cooperative activities in a way that allows a pair of animals (or people) that have a potential conflict of interest to arrive at a cooperative outcome rather than a competitive outcome.

Darwin (1872) reviewed the facial and bodily expressions of many animals, especially mammals, and frequently mentioned how pleasure is expressed. He writes, "With the lower animals we see the same principle of pleasure derived from contact in association with love. Dogs and cats manifestly take pleasure in rubbing against their masters and mistresses, and in being rubbed or patted by them. Many kinds of monkeys … delight in fondling and being fondled by each other, and by persons to whom they are attached" [31, pp. 215–216]. Darwin also recognized pleasure through song: "We can plainly perceive, with some of the lower animals, that the males employ their voices to please the females, and that they themselves take pleasure in their own vocal utterances" [31, pp. 87–88]. The pleasure associated with physical and vocal intimacy that Darwin describes is the key feature to my concept of teamwork.

I have further hypothesized that the act of cooperation itself is pleasurable. As a human analogy, consider the difference in pleasure between making an "Alley-Oop pass" in basketball compared with making two foul shots, both of which yield the same two points. Of course, every member of a basketball team feels some pleasure when two foul shots are successful, but the pleasure experienced is even greater if the two points are obtained with a beautiful acrobatic pass followed by a teammate's dunk at the basket. This is invariably followed by high-fives all around. A similar point could be made about the pleasure of scoring a goal during regulation play in soccer compared with scoring a goal during sudden death overtime.

Together with colleagues, I have published game-theoretic mathematical models showing how cooperation attained via the reciprocal exchange of pleasure, including homosexuality, leads to cooperative solutions to games that involve conflicts of interest between the parties (Roughgarden et al., 2006; Akçay et al., 2009; Akçay and Roughgarden, 2011; Roughgarden, 2012b).

Finally, I would like to remark on what might explain the polymorphism in sexual orientation: the ratio of gays to straights? Indeed, a problem if homosexuality supplies advantages becomes why is everyone not homosexual, as in bonobos and Japanese macaques.

The polymorphism between straights and gays may be maintained by frequency-dependent selection between two alternative strategies of within-sex relations, each of which provides survival or reproductive advantages. Members of the straight morph may build alliances based on a meritocracy and/or the exchange of power, and members of the gay morph may build alliances based on the exchange of pleasure. Either strategy, if common enough, would be subject to increase when rare by the other, leading to a polymorphism.

Furthermore, the conflict likely to occur between these alternative morphs for same-sex relations is possibly the basis of homophobia. Alliances based on the exchange of pleasure may threaten to subvert alliances based on the exchange of socially constructed concepts of merit and power. Same-sex pleasure-based alliances would then be subject to suppression seemingly justified with a disparaging narrative propounded those with the power to define normalcy.

SUMMARY

1. Homosexual behavior occurs naturally in many species of mammals, and also in insects. Among primates, homosexuality is an evolutionary innovation originating when the anthropoid lineage split from the prosimian linage, and it becomes particularly prominent in the complex societies of the old world primates.
2. Many species possess multiple genders: multiple morphs within each sex.
3. Transgender species have been documented, especially in hummingbirds.
4. Homosexual behavior and transgender expression is documented across all present-day human cultures, throughout recorded history, including the Bible and other religious texts, and in Paleolithic drawings and artifacts.
5. A transgender "third sex" exists in many cultures, and it has official status in India and its neighbors.
6. Homosexuality became a Western category of human personal identity in the mid-1800s.
7. Investigators employ many inconsistent definitions of homosexuality.
8. Gay and lesbian people cluster in families.
9. Despite 30 years of research, a gay gene has not been located in the human genome.
10. Despite 30 years of research, the brains of homosexual men have not been shown to resemble the brains of women.
11. The brains of transgender people resemble the brains of the gender they identify with and not with the brains corresponding to their biological sex.

12. The brains of transgender people develop reflecting the timing of sex hormones at different stages during fetal growth.
13. Gender identity may exist in the brain as a "cognitive lens" that controls who to focus on as a developmental "tutor." Transgender identity is the acceptance of a tutor from the opposite sex.
14. Gender identity has developed by the time of birth, and sexual orientation develops later during the first few years of infancy.
15. Homosexuality and transgender are too common to be considered genetic diseases.
16. The fertility cost of male homosexuality is as much as 50% in contemporary Western culture and much less or nonexistent in other cultures.
17. The theory that the fertility cost of male homosexual behavior is offset by a fecundity advantage to the mothers of homosexual children has weak or no supportive evidence.
18. Transgender expression, but not homosexual behavior, might have evolved through kin selection in cultures with a third sex, such as the fa'afafine of Samoa.
19. It is improbable that homosexual behavior is selectively neutral.
20. Homosexual behavior appears to be selectively advantageous because it produces alliances and partnerships.
21. Homosexual behavior may be a special case of various forms of physically intimate behavior that promote cooperation through the reciprocal sharing of pleasure.
22. The homosexual/heterosexual polymorphism may result from frequency-dependent selection between alternative same-sex alliance strategies: alliances based on a socially-constructed meritocracy and alliances based on a mutual exchange of pleasure. Homophobia might be a byproduct of competition between these types of alliances.

ACKNOWLEDGMENT

I thank Milton Diamond, Sebastian Donovan, and Gillian Einstein for helpful comments that greatly improved the manuscript.

REFERENCES

Akçay, E., Roughgarden, J., 2011. The evolution of payoff matrices: providing incentives to cooperate. Proceedings of the Royal Society of London, Series B: Biological Sciences 278, 2198–2206. http://dx.doi.org/10.1098/rspb.2010.2105.

Akçay, E., Van Cleve, J., Feldman, M.W., Roughgarden, J., 2009. A theory for the evolution of other-regard integrating proximate and ultimate perspectives. Proceedings of the National Academy of Sciences of the United States of America 106, 19061–19066.

Allen, L.S., Hines, M., Shryne, J.E., Gorski, R.A., 1989. Two sexually dimorphic cell groups in the human brain. Journal of Neuroscience 9, 497–506.

Bagemihl, B., 1999. Biological Exuberance: Animal Homosexuality and Natural Diversity. St. Martin's Press, New York.

Bailey, J., Bell, A., 1993. Familiality of female and male homosexuality. Behavioral Genetics 23, 313–322.

Bailey, J., Benishay, D., 1993. Familial aggregation of female sexual orientation. American Journal of Psychiatry 150, 272–277.

Bailey, J.M., Pillard, R.C., 1991. A genetic study of male sexual orientation. Archives of General Psychiatry 48, 1089–1096.

Bailey, J.M., Pillard, R.C., Neale, M.C., Agyei, Y., 1993. Heritable factors influence sexual orientation in women. Archives of General Psychiatry 50, 217–223.

Bailey, J.M., Dunne, M.P., Martin, N.G., 2000. Genetic and environmental influences on sexual orientation and its correlates in an Australian twin sample. Journal of Personality and Social Psychology 78, 524–536.

Baker, R., Bellis, M., 1995. Human Sperm Competition: Copulation, Masturbation, and Infidelity. Chapman and Hall, New York.

Bao, A.M., Swaab, D.F., 2011. Sexual differentiation of the human brain: relation to gender identity, sexual orientation and neuropsychiatric disorders. Frontiers in Neuroendocrinology 32, 214–226.

Barber, N., 1998. Ecological and psychosocial correlates of male homosexuality: a cross-cultural investigation. Journal of Cross-Cultural Psychology 29, 387–401.

Barlow, G., 2000. The Cichlid Fishes. Perseus Publishing, p. 145.

Bartlett, N.H., Vasey, P.L., 2006. A retrospective study of childhood gender: atypical behavior in Samoan fa'afafine. Archives of Sexual Behavior 35, 559–566.

Beachy, R., 2010. The German Invention of homosexuality. The Journal of Modern History 82, 801–838.

Belzner, S., Voigt, C., Catchpole, C.K., Leitner, S., 2009. Song learning in domesticated canaries in a restricted acoustic environment. Proceedings of the Royal Society of London, Series B: Biological Sciences 276, 2881–2886. http://dx.doi.org/10.1098/rspb.2009.0669.

Bengtsson, S.L., Nagy, Z., Skare, S., Forsman, L., Forssberg, H., Ullen, F., 2005. Extensive piano practicing has regionally specific effects on white matter development. Nature Neuroscience 8, 1148–1150.

Berglund, H., Lindström, P., Dhejne-Helmy, C., Savic, I., 2008. Male-to-female transsexuals show sex-atypical hypothalamus activation when smelling odorous steroids. Cerebral Cortex 18, 1900–1908.

Bermudez, P., Zatorre, R.J., 2005. Differences in gray matter between musicians and nonmusicians. In: Avanzini, G., Koelsch, S., Lopez, L., Majno, M. (Eds.), Neurosciences and Music II: From Perception to Performance, pp. 395–399.

Bermudez, P., Lerch, J.P., Evans, A.C., Zatorre, R.J., 2009. Neuroanatomical correlates of musicianship as revealed by cortical thickness and voxel-based morphometry. Cerebral Cortex 19, 1583–1596.

Besnier, N., 1994. Polynesian gender liminality. In: Herdt, G. (Ed.), Third Sex, Third Gender. Zone, New York, pp. 285–328.

Blanchard, R., Bogaert, A.F., 1996. Homosexuality in men and number of older brothers. American Journal of Psychiatry 153, 27–31.

Blanchard, R., Klassen, P., 1997. H-Y antigen and homosexuality in men. Journal of Theoretical Biology 185, 373–378.

Blanchard, R., 1989. The concept of autogynephilia and typology of male gender dysphoria. Journal of Nervous and Mental Disease 177, 616–623.

Blanchard, R., 2008. Review and theory of handedness, birth order, and homosexuality in men. Laterality 13, 51–70.

Bleiweiss, R., 1992. Widespread polychromatism in female sunangel hummingbirds (*Heliangelus: Trochilidae*). Biological Journal of the Linnean Society 45, 291–314.

Bleiweiss, R., 1999. Joint effects of feeding and breeding behavior on trophic dimorphism in hummingbirds. Proceedings of the Royal Society of London, Series B: Biological Sciences 266, 2491–2497.

Bleiweiss, R., 2001. Asymmetrical expression of transsexual phenotypes in hummingbirds. Proceedings of the Royal Society of London, Series B: Biological Sciences 268, 639–646.

Bobrow, D., Bailey, J.M., 2001. Is male homosexuality maintained via kin selection? Evolution and Human Behavior 22, 361–368.

Bogaert, A.F., 2006. Biological versus nonbiological older brothers and men's sexual orientation. Proceedings of the National Academy of Sciences of the United States of America 103, 10771–10774.

Burr, C., 1996. A Separate Creation; The Search for the Biological Origins of Sexual Orientation. Hyperion, New York.

Byne, W., Parsons, B., 1993a. Human sexual orientation: the biologic theories reappraised. Archives of General Psychiatry 50, 228–239.

Byne, W., Parsons, B., 1993b. Human homosexuality: the biological theories reappraised. Archives of General Psychiatry 50, 228–239.

Byne, W., Tobet, S., Mattiace, L., Lasco, M.S., Kemether, E., Edgar, M.A., Morgello, S., Buchsbaum, M.S., Jones, L.B., 2001. The interstitial nuclei of the human anterior hypothalamus: an investigation of variation within sex, sexual orientation and HIV status. Hormones & Behavior 40, 86–92.

Camperio Ciani, A., Corna, F., Capiluppi, C., 2004. Evidence for maternally inherited factors favouring male homosexuality and promoting female fecundity. Proceedings of the Royal Society of London, Series B: Biological Sciences 271, 2217–2221.

Camperio Ciani, A., Cermelli, P., Zanzotto, G., 2008. Sexually antagonistic selection in human male homosexuality. PLoS One 3 (6), e2282. http://dx.doi.org/10.1371/journal.pone.0002282.

Camperio Ciani, A., Iemmola, F., Blecher, S.R., 2009. Genetic factors increase fecundity in female maternal relatives of bisexual men as in homosexuals. Journal of Sexual Medicine 6, 449–455.

Chakrapani, V., Newman, P.A., Shunmugam, M., McLuckie, A., Melwin, F., 2007. Structural violence against kothi–identified men who have sex with men in Chennai, India: a qualitative investigation. AIDS Education and Prevention 19, 346–364.

Colapinto, J., 2000. As Nature Made Him: The Boy Who Was Raised as a Girl. HarperCollins.

Crinion, J.T., Green, D.W., Chung, R., Ali, N., Grogan, A., Price, G.R., Price, C.J., 2009. Neuroanatomical markers of speaking Chinese. Human Brain Mapping 30, 4108–4115.

Darwin, C., 1871. The Descent of Man and Selection in Relation to Sex. Volumes I. and II.. John Murray, London.

Darwin, C., 1872. The Expression of the Emotions in Man and Animals. John Murray, London, UK.

Dawood, K., Michael Bailey, J., Martin, N.G., 2009. Genetic and environmental influences on sexual orientation. In: Handbook of Behavior Genetics. Springer, New York, pp. 269–279.

Dean, L., Meyer, I., Robinson, K., Sell, R., Sember, R., Silenzio, V., Bowen, D., Bradford, J., Rothblum, E., Scout, M., White, J., Dunn, P., Lawrence, A., Wolfe, D., Xavier, J., 2000. Lesbian, gay, bisexual, and transgender health: findings and concerns. Journal of the Gay and Lesbian Medical Association 4, 101–151.

Dickemann, M., 1993. Reproductive strategies and gender construction: an evolutionary view of homosexualities. Journal of Homosexuality 24 (3/4), 55–71.

Doniger, W., 2009. The Hindus: An Alternative History. The Penguin Press, New York.

Dover, K.J., 1978. Greek Homosexuality. Harvard University Press, Cambridge, MA.

Elbert, T., Pantev, C., Wienbruch, C., Rockstroh, B., Taub, E., 1995. Increased cortical representation of the fingers of the left hand in string players. Science 270, 305–306.

Ellis, L., Ames, M.A., 1987. Neurohormonal functioning and sexual orientation: a theory of homosexuality/heterosexuality. Psychological Bulletin 101, 233–258.

Essock-Vitale, S., McGuire, M., 1988. What 70 million years hath wrought: sexual histories and reproductive success of a random sample of American women. In: Betzig, Mulder, M.B., Turke, P. (Eds.), Human Reproductive Behavior: A Darwinian Perspective. Cambridge University Press, pp. 221–235.

Feldman, M.W., 1972. Selection for linkage modification. I. Random mating populations. Theoretical Population Biology 3, 324–346.

Futuyma, D., Risch, S., 1984. Sexual orientation, sociobiology, and evolution. Journal of Homosexuality 9, 157–168.

Garcia-Falgueras, A., Swaab, D.F., 2008. A sex difference in the hypothalamic uncinate nucleus: relationship to gender identity. Brain 131, 3132–3146.

Gaser, C., Schlaug, G., 2003. Brain structures differ between musicians and non-musicians. Journal of Neuroscience 23, 9240–9245.

Gates, G., 2011. How Many People Are Lesbian, Gay, Bisexual, and Transgender? The Williams Institute. UCLA, Los Angeles. http://williamsinstitute.law.ucla.edu/research/census-lgbt-demographics-studies/how-many-people-are-lesbian-gay-bisexual-and-transgender/.

Gates, G., 2012. LGBT identity: a demographer's perspective. Loyola of Los Angeles Law Review 45, 693–714. Available at: http://digitalcommons.lmu.edu/llr/vol45/iss3/2.

Gavrilets, S., Rice, W.R., 2006. Genetic models of homosexuality: generating testable predictions. Proceedings of the Royal Society of London, Series B: Biological Sciences 273, 3031–3038. http://dx.doi.org/10.1098/rspb. 2006.3684.

Gizewski, E.R., Krause, E., Schlamann, M., Happich, F., Ladd, M.E., Forsting, M., Senf, W., 2009. Specific cerebral activation due to visual erotic stimuli in male-to-female transsexuals compared with male and female controls: an fMRI study. Journal of Sexual Medicine 6, 440–448.

Greenberg, D., 1988. The Construction of Homosexuality. University of Chicago Press.

Hahn, A., Kranz, G.S., Küblböck, M., Kaufmann, U., Ganger, S., Hummer, A., Lanzenberger, R., 2015. Structural connectivity networks of transgender people. Cerebral Cortex 25, 3527–3534. http://dx.doi.org/10.1093/cercor/bhu194.

Halperin, D.M., 1990. One Hundred Years of Homosexuality: And Other Essays on Greek Love. Routledge, New York.

Hamer, D., Hu, S., Magnuson, V., Hu, N., Pattatucci, A., 1993. A linkage between DNA markers on the X chromosome and male sexual orientation. Science 261, 321–327.

Herdt, G. (Ed.), 1994. Third Sex Third Gender: Beyond Sexual Dimorphism in Culture and History. Zone Books, New York.

Hoskins, J.L., Ritchie, M.G., Bailey, N.W., 2015. A test of genetic models for the evolutionary maintenance of same-sex sexual behaviour. Proceedings of the Royal Society of London, Series B: Biological Sciences 282. http://dx.doi.org/10.1098/rspb.2015.0429.

Hu, S., Pattatucci, A., Patterson, C., Li, L., Fulker, D., Cherny, S., Kruglyak, L., Hamer, D., 1995. Linkage between sexual orientation and chromosome Xq28 in males but not in females. Nature Genetics 11, 248–256.

Iemmola, F., Camperio Ciani, A., 2009. New evidence of genetic factors influencing sexual orientation in men: female fecundity increase in the maternal line. Archives of Sexual Behavior 38, 393–399.

Isomura, S., Mizogami, M., 1992. The low rate of HIV infection in Japanese homosexual and bisexual men: an analysis of HIV seroprevalence and behavioral risk factors. AIDS 6, 501–503.

Jannini, E.A., Blanchard, R., Camperio-Ciani, A., Bancroft, J., 2010. Male homosexuality: nature or culture? Journal of Sexual Medicine 7, 3245–3253.

Jung, P., Coray, J. (Eds.), 2001. Sexual Diversity and Catholicism: Toward the Development of Moral Theology. The Liturgical Press.

Jung, P., Vigen, A. (Eds.), 2010. God, Science, Sex, Gender: An Interdisciplinary Approach to Christian Ethics. University of Illinois Press.

Kanai, R., Feilden, T., Firth, C., Rees, G., 2011. Political orientations are correlated with brain structure in young adults. Current Biology 21, 677–680.

Katz, J., 1995. The Invention of Heterosexuality. Dutton.

Kendler, K., Thornton, L., Gilman, S., Kessler, R., 2000. Sexual orientation in a U.S. National sample of twin and nontwin sibling pairs. American Journal of Psychiatry 157 (11), 1843–1846.

King, M., McDonald, E., 1992. Homosexuals who are twins: a study of 46 probands. British Journal of Psychiatry 160, 407–409.

King, M.D., Green, J., Osborn, D.P.J., Arkell, J., Hetherton, J., Pereira, E., 2005. Family size in white gay and heterosexual men. Archives of Sexual Behavior 34, 117–122.

Kirkpatrick, R., 2000. The evolution of human homosexual behavior. Current Anthropology 41, 385–413.

Kranz, G.S., Hahn, A., Kaufmann, U., Küblböck, M., Hummer, A., Ganger, S., Lanzenberger, R., 2014. White matter microstructure in transsexuals and controls investigated by diffusion tensor imaging. The Journal of Neuroscience 34 (46), 15466–15475.

Kueffler, M., 2001. The Manly Eunuch: Masculinity, Gender Ambiguity, and Christian Ideology in Late Antiquity. University of Chicago Press, Chicago.

Långström, N., Rahman, Q., Carlström, E., Lichtenstein, P., 2010. Genetic and environmental effects on same-sex sexual behavior: a population study of twins in Sweden. Archives of Sexual Behavior 39, 75–80.

LeVay, S., 1991. A difference in hypothalamic structure between heterosexual and homo- sexual men. Science 253, 1034–1037.

Moser, C., 2010. Blanchard's autogynephilia theory: a critique. Journal of Homosexuality 57 (6), 790–809. http://dx.doi.org/10.1080/00918369.2010.486241.

Muscarella, F., 2000. The evolution of homoerotic behavior in humans. Journal of Homosexuality 40, 51–77.

Mustanski, B.S., Chivers, M.L., Bailey, J.M., 2002. A critical review of recent biological research on human sexual orientation. Annual Review of Sex Research 13, 89–140.

Mustanski, B.S., Dupree, M.G., Nievergelt, C.M., Bocklandt, S., Schork, N.J., Hamer, D.H., 2005. A genomewide scan of male sexual orientation. Human Genetics 116, 272–278.

Nanda, S., 1999. Neither Man nor Woman: The Hijras of India, second ed. Wadsworth Publishing Company, Belmont, CA.

Nash, G., 2001. The subversive male: homosexual and bestial images on European Mesolithic rock art. In: Bevan, L. (Ed.), Indecent Exposure: Sexuality, Society and the Archaeological Record. Cruithne, Glasgow, pp. 43–55.

Nawata, H., Ogomori, K., Tanaka, M., Nishimura, R., Urashima, H., Yano, R., Takano, K., Kuwabara, Y., 2010. Regional cerebral blood flow changes in female to male gender identity disorder. Psychiatry and Clinical Neurosciences 64, 157–161.

Nuttbrock, L., Bockting, W., Mason, M., Hwahng, S., Rosenblum, A., Macri, M., Becker, J., 2011. A further assessment of Blanchard's typology of homosexual versus non-homosexual or autogynephilic gender dysphoria. Archives of Sexual Behavior 40, 247–257. http://dx.doi.org/10.1007/s10508-009-9579-2.

Parish, A., 1996. Female relationships in bonobos (*Pan paniscus*), evidence for bonding, cooperation, and female dominance in a male-philopatric species. Human Nature 7, 61–96.

Paus, T., 2005. Mapping brain maturation and cognitive development during adolescence. Trends in Cognitive Sciences 9, 60–68.

Peletz, M., 2006. Transgenderism and gender pluralism in Southeast Asia since early modern times. Current Anthropology 47, 309–340.

Penrose, W., 2001. Hidden in history: Female homoeroticism and women of a "third nature" in the South Asian past. Journal of the History of Sexuality 10, 3–39.

Pillard, R., Weinrich, J., 1986. Evidence of familial nature of male homosexuality. Archives of General Psychiatry 43, 808–812.

Poasa, K., 1992. The Samoan Fa'afafine: one case study and discussion of trans- sexualism. Journal of Psychology and Human Sexuality 5 (3), 39–51.

Rahman, Q., Hull, M., 2005. An empirical test of the kin selection hypothesis for male homosexuality. Archives of Sexual Behavior 34, 461–467.

Ramagopalan, S.V., Dyment, D.A., Handunnetthi, L., Rice, G.P., Ebers, G.C., 2010. A genome-wide scan of male sexual orientation. Journal of Human Genetics 55, 131–132.

Rametti, G., Carrillo, B., Gomez-Gil, E., Junque, C., Segovia, S., Gomez, A., Guillamon, A., 2011a. White matter microstructure in female to male transsexuals before cross-sex hormonal treatment. A diffusion tensor imaging study. Journal of Psychiatric Research 45, 199–204.

Rametti, G., Carrillo, B., Gomez-Gil, E., Junque, C., Zubiarre-Elorza, L., Segovia, S., Gomez, A., Guillamon, A., 2011b. The microstructure of white matter in male to female transsexuals before cross-sex hormonal treatment. A DTI study. Journal of Psychiatric Research 45, 949–954.

Rice, G., Anderson, C., Risch, N., Ebers, G., 1999. Male homosexuality: absence of linkage to microsatellite markers at Xq28. Science 284, 665–667.

Roscoe, W., 1991. The Zuni Man-woman. University of New Mexico Press, Albuquerque.

Roscoe, W., 1996. Priests of the goddess: gender transgression in ancient religion. History of Religions 35, 195–230.

Roscoe, W., 1998. Changing Ones: Third and Fourth Genders in Native North America. St. Martin's Press, New York.

Roughgarden, J., Oishi, M., Akçay, E., 2006. Reproductive social behavior: cooperative games to replace sexual selection. Science 311, 965–969.

Roughgarden, J., Adkins-Regan, E., Akçay, E., Crawford, J.C., Gadagkar, R., Griffith, S.C., Hinde, C.A., Hoquet, T., O'Connor, C., Prokop, Z.M., Prum, R.O., Shafir, S., Snow, S.S., Taylor, D., Van Cleve, J., Weisberg, M., 2015. Sexual selection studies: a NESCent catalyst meeting. PeerJ PrePrints 3, e680v3. http://dx.doi.org/10.7287/peerj.preprints.680v3.

Roughgarden, J., 2004. Evolution's Rainbow: Diversity, Gender, and Sexuality in Nature and People. University of California Press,

Berkeley, CA. Portuguese translation, 2005, published by editoria Planta, Brazil. Korean translation, 2010, published by Puriwa Ipari Publishing Co., Seoul, Korea.

Roughgarden, J., 2009. The Genial Gene: Deconstructing Darwinian Selfishness. University of California Press, Berkeley, CA. French translation, 2012, published by Le Seuil, Paris.

Roughgarden, J., 2012a. The social selection alternative to sexual selection. Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences 367, 2294–2303.

Roughgarden, J., 2012b. Teamwork, pleasure and bargaining in animal social behaviour. Journal of Evolutionary Biology 25, 1454–1462. http://dx.doi.org/10.1111/j.1420-9101.2012.02505.x.

Roughgarden, J., 2015. Sexual selection: is anything left? In: Hoquet, T. (Ed.), Current Perspectives on Sexual Selection: What's Left after Darwin? Springer Verlag, pp. 85–102.

Sanders, A.R., Martin, E.R., Beecham, G.W., Guo, S., Dawood, K., Rieger, G., Badner, J.A., Gershon, E.S., Krishnappa, R.S., Kolundzija, A.B., Duan, J., Gejman, P.V., Bailey, J.M., 2015. Genome-wide scan demonstrates significant linkage for male sexual orientation. Psychological Medicine 45, 1379–1388. http://dx.doi.org/10.1017/S0033291714002451.

Saraswat, A., Weinand, J.D., Safer, J.D., 2015. Evidence supporting the biologic nature of gender identity. Endocrine Practice 21, 199–204.

Savic, I., Arver, S., 2011. Sex dimorphism of the brain in male-to-female transsexuals. Cerebral Cortex 21, 2525–2533.

Savic, I., Lindström, P., 2008. PET and MRI show differences in cerebral asymmetry and functional connectivity between homo- and heterosexual subjects. Proceedings of the National Academy of Sciences of the United States of America 105, 9403–9408.

Schmidt, J., 2003. Paradise lost? Social change and fa'afafine in Samoa. Current Sociology 51, 417–432.

Schoning, S., Engelien, A., Bauer, C., Kugel, H., Kersting, A., Roestel, C., Zwitser- lood, P., Pyka, M., Dannlowski, U., Lehmann, W., et al., 2010. Neuroimaging differences in spatial cognition between men and male-to-female trans- sexuals before and during hormone therapy. Journal of Sexual Medicine 7, 1858–1867.

Schwartz, G., Kim, R.M., Kolundziji, A.B., Rieger, G., Sanders, A.R., 2010. Biodemographic and physical correlates of sexual orientation in men. Archives of Sexual Behavior 39, 93–109.

Simon, L., Kozak, L.R., Simon, V., Czobor, P., Unoka, Z., Szabo, A., Csukly, G., 2013. Regional grey matter structure differences between transsexuals and healthy controls – a voxel based morphometry study. PloS One 8, e83947.

Smith, Y.L., van Goozen, S.H., Kuiper, A.J., Cohen-Kettenis, P.T., 2005. Transsexual subtypes: clinical and theoretical significance. Psychiatry Research 137, 151–160.

Sommer, V., Vasey, P. (Eds.), 2006. Homosexual Behaviour in Animals: An Evolutionary Perspective. Cambridge University Press.

Swaab, D.F., Garcia-Falgueras, A., 2009. Sexual differentiation of the human brain in relation to gender identity and sexual orientation. Functional Neurology 24, 17–28.

Swaab, D., Zhou, J.-N., Ehlhart, T., Hofman, M., 1994. Development of vasoactive intestinal polypeptide neurons in the human suprachiasmatic nucleus in relation to birth and sex. Developmental Brain Research 79, 249–259.

Swaab, D., Gooren, L., Hofman, M., 1995. Brain research, gender, and sexual orientation. Journal of Homosexuality 28, 283–301.

Van de Ven, P., Rodden, P., Crawford, J., Kippax, S., 1997. A comparative demographic and sexual profile of older homosexually active men. Journal of Sex Research 34, 349–360.

Vasey, P.L., VanderLaan, D.P., 2009. Materteral and avuncular tendencies in Samoa: a comparative study of women, men, and *fa'afafine*. Human Nature 20, 269–281.

Vasey, P., Chapais, B., Gauthier, C., 1998. Mounting interactions between female Japanese macaques: testing the influence of dominance and aggression. Ethology 104, 387–398.

Vasey, P.L., Pocock, D.S., VanderLaan, D.P., 2007. Kin selection and male androphilia in Samoan *fa'afafine*. Evolution and Human Behavior 28, 159–167.

Vasey, P., 1995. Homosexual behavior in primates: a review of evidence and theory. Journal of Primatology 16, 173–204.

Vasey, P., 1996. Interventions and alliance formation between female Japanese macaques, *Macaca fuscata*, during homosexual consortships. Animal Behaviour 52, 539–551.

Vasey, P., 1998. Intimate sexual relations in prehistory: lessons from the Japanese macaques. World Archaeology 29, 407–425.

Whitam, F., Diamond, M., Martin, J., 1993. Homosexual orientation in twins: a report on 61 pairs and three triplet sets. Archives of Sexual Behavior 22, 187–206.

Williams, W., 1986. The Spirit and the Flesh: Sexual Diversity in American Indian Culture. Beacon Press, Boston.

Williams, H., 2008. Bird song and singing behavior. In: Ziegler, H.P., Marler, P. (Eds.), The Neuroscience of Bird Song. Cambridge University Press, Cambridge.

Wilson, D.S., Wilson, E.O., 2007. Rethinking the theoretical foundation of sociobiology. Quarterly Review of Biology 82, 327–348.

Wilson, E.O., 1975. Sociobiology: The New Synthesis. Harvard University Press, Cambridge, MA see especially page 555 for a discussion of homosexuality.

Wilson, E.O., May 03, 1979. Gay as normal: homosexuality and human nature: a sociobiological view. Advocate 15, 18.

Yankelovich Partners, 1994. A Yankelovich MONITOR Perspective on Gays and Lesbians (Norwalk, Connecticut).

Zatorre, R.J., Belin, P., Penhune, V.B., 2002. Structure and function of auditory cortex: music and speech. Trends in Cognitive Sciences 6, 37–46.

Zhou, J.N., Hofman, M.A., Gooren, L.J., Swaab, D.F., 1995. A sex difference in the human brain and its relation to transsexuality. Nature 378, 68–70.

Zwilling, L., Sweet, M.J., 1996. Like a city ablaze: the third sex and the creation of sexuality in Jain religious literature. Journal of the History of Sexuality 613, 359–384.

Chapter 31

The Roots and Individual Diversity of Addiction

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LIST OF ABBREVIATIONS

ADH Alcohol dehydrogenase
ADE Alcohol deprivation effect
ASI Alcohol Composite Index of the Addiction Severity Index
CPP Conditioned place preference
CRH Corticotropin releasing hormone
CTA Conditioned taste aversion
DSM-V *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition
EPM Elevated plus maze
GWAS Genome-wide association studies
HPA Hypothalamic-pituitary adrenal axis
ICD *International Statistical Classification of Diseases and Related Health Problems*
ICSS Intracranial self-stimulation
MDMA 3,4-Methylenedioxymethamphetamine
mGluR5 Metabotropic glutamate receptor type 5
NAc Nucleus accumbens
PFC Prefrontal cortex

INTRODUCTION

In medicine or psychology, the detailed report of the symptoms, signs, diagnosis, and treatment obtained from patients with addictive problems is known as a "case report." While it is understood that these are anecdotal accounts, ultimately they might provide insight into the disease and the treatments for it. At this point, as a first step, personal stories can also help us identify questions that we will want to answer in our search for the roots and individual diversity of addiction. Here are two stories.

Jörg never liked school; he was not good, so he soon decided to not continue his studies. He always wanted something that could give him easy money without great effort. Having left school, it was time to find a job, and he found it: Jörg started selling drugs on the street. This decision was motivated by his twin brother, who at that time worked as a manager for famous music bands, and thus had a direct contact with any kind of addictive drugs. During the following years, Jörg (with his brother) continuously succeeded in his "business" and had a lot of money and friends. His life was based on going to parties all night long and consuming addictive drugs (cocaine, cannabis, amphetamine, and designer drugs) without control. All of a sudden, this situation radically changed when he was arrested by the police. After spending about 5 years in prison, his life, obviously, would never be the same. He had no money, he could not find a job, and his brother (always very attached to him) became seriously ill. Now, the over-50-year-old Jörg works as a dishwasher in a restaurant, many times he cannot pay the rent of his apartment, and he continuously smokes marijuana. Surprisingly, this life does not seem to bother him much, as he always looks happy, too happy. Moreover, sometimes, he seems to be "confused" and "disconnected" from the real world. For example, he forgets his keys in the apartment, gets lost when driving, or forgets to wake up in the morning to go to work. Some of the people that know him (like neighbors) think that the reason for this illogic unawareness and confusion is that he smokes too much marijuana; however, friends close to him say that "he was always like that, a bit short." But at the present, just one thing is clear for all of the people that know Jörg: he is getting worse and worse.

The story of Andrew is different. His life started to be difficult in childhood. His parents did not get along together, and a few years after his birth, the mother left the country with Andrew. He was a very hyperactive child, and this behavior caused him a lot of problems, particularly in the school. Indeed, he received different pharmacological treatments on

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00031-4

several occasions, without ever achieving a complete success. After finishing school, he constantly tried different jobs (always independent), and at some point, he started selling drugs on the street in parallel. His dynamic and hyperactive personality fit so perfectly in this environment that he soon really succeeded and earned big amounts of money. His work was then progressive neglected, and his behavior became characterized by a permanent compulsivity and loss of control over his life: he could not refrain from taking drugs, and he could not refrain from wasting money. But, as with Jörg, he was sent to prison. However, this experience did not change his life as one would expect. Andrew started working independently, and he kept consuming drugs in a more or less compulsive way. Interestingly, as soon as he started finding some stability in his job and earning money, he progressively started consuming more and more drugs. Over the next years, his life was characterized by repeated cycles of binge intoxications, followed by short periods of abstinence that affected him strongly psychologically, physically, and socially: his mood became very unstable, irritable (up to aggressiveness), and depressive; he appeared tired and thin, and he lost contact with some of his friends. Andrew reached such a point that he almost ruined his own business. Now he has been in abstinence from psychostimulants for more than one year and has changed his life completely: he is focused on his business again; he has healthy habits like practicing sports and keeping a healthy diet, and he has contact with some of his friends again. Although he still suffers the economic and health consequences of that period, he has mostly recovered psychologically, and more importantly, he is highly motivated and reinforced by his achievement.

These stories exemplify clearly the problem of addiction. More importantly, they reflect the complexity of the disorder. How should one classify this? The reader might find it interesting to identify symptoms of addiction from these two stories according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V). The DSM-V (American Psychiatric Association, 2013) specifies 11 symptoms: the presence of two to three symptoms within a 12-month period indicates a mild disorder, four to five a moderate one, and six or more a severe disorder. These criteria include the following:

1. the drug is often taken in larger amounts or over a longer period than was intended,
2. there is a persistent desire or unsuccessful efforts to cut down or control drug use,
3. a great deal of time is spent in activities necessary to obtain the drug, use the drug, or recover from its effects,
4. craving or a strong desire or urge to use the drug,
5. recurrent drug use resulting in a failure to fulfill major role obligations at work, school, or home,
6. continued drug use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the drug,
7. important social, occupational, or recreational activities are given up or reduced because of drug use,
8. recurrent drug use in situations in which it is physically hazardous,
9. drug use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the drug,
10. tolerance, as defined by either of the following:
    a. a need for markedly increased amounts of the drug to achieve intoxication or desired effect,
    b. a markedly diminished effect with continued use of the same amount of the drug.
11. withdrawal, as manifested by either of the following:
    a. the characteristic withdrawal symptoms for the drug,
    b. the drug (or a closely related substance) is taken to relieve or avoid withdrawal symptoms.

If the reader took the time to diagnose Jörg and Andrew according to the DSM-V criteria, he/she might have realized that both can be diagnosed as substance abusers regardless of how and why they ended up in this addictive behavior. From their stories, one can easily notice that different factors influenced the development of such disorder. Thus, was Jörg environmentally influenced, being surrounded by drugs, or had he some neurocognitive deficits that predisposed him to addiction? In the case of Andrew, did his early adverse life experiences impact on his later addictive behaviors, or was his hyperactive personality more influential? We cannot answer these questions because addiction cannot be solely attributed to one or another cause. Rather, addiction has many roots, and it varies across individuals. In this chapter, I will try to give an overview about the roots and individual diversity of addiction. To that end, I will first show that addiction is an old phenomenon that has always been present across history. Then, I will introduce the psychological constructs through which drugs gradually modify behavior during the transition to addiction, and the resulting specific genotypes or behavioral patterns associated to addiction. Finally, I will briefly go over biological, psychological (personality), environmental, and genetic vulnerability factors that predispose the individuals to addictive disorders.

ADDICTIVE BEHAVIOR IN HUMANS THROUGHOUT HISTORY

Addictive Drugs in Prehistory and Patterns of Use

The use of addictive drugs is an old phenomenon in human history. Exemplifying this fact, Ötzi, the oldest natural mummy found in Europe from the late Neolithic (around 5300 years ago, found in the Alps by two German hikers in 1991) carried in his bag some plants and substances

together with a polypore fungus with antibacterial and hemostatic properties (Kutschera and Rom, 2000). Further, from the oral, written, or art references found by archaeologists and anthropologists, the human's relationship with addictive drugs has been recognized in almost all cultural groups and has persisted across the prehistoric era. But, to what extent were drugs used? The answer is clear: since those ancient times till now, the driving force of such a relationship between humans and psychoactive substances has been psychological, with the final purpose of altering the states of consciousness.

In this regard, it has been suggested that the use of drugs may have played an additional evolutionary role in mental or brain development, and in the origin of language and religion, an idea proposed by Terence Kemp McKenna. He wrote about the theoretical origins of human consciousness, and his work culminated in the formulation of the "stoned ape" theory of human evolution. In this theory, he argued that the consumption of mushrooms would be triggering activity in the language-forming region of the brain, resulting in an evolutionary advantage leading to the development of language, projective imagination, the arts, religion, philosophy, science, and all of human culture (Sheldrake et al., 1998).

During prehistoric times, the use of substances influencing mood and thinking processes was restricted to particular environmental conditions and influenced by three dominant patterns of use: religious, medicinal, and recreational. Some of the most commonly used substances for religious or medicinal purposes were the mushroom fly agaric (*Amanita muscaria*), opium (*Papaver somniferum*), marijuana (*Cannabis sativa*), the peyote cactus (*Lophophora williamsi*), alcohol, tobacco (*Nicotiana*), and cocaine (*Erythroxylon coca*). The consumption of fly agaric, believed to have been used in Neolithic times and later in Central Asia for at least 4000 years, caused states of spiritual introspection; marijuana was consumed together with the peyote cactus and mescaline by ancient Aztecs and other Mexican Indians 4000 years ago and in India near 1500 BC for their hallucinogenic properties; priests from Ethiopia used to roast and boil coffee beans to stay awake through nights of prayer. We also know that alcohol was used by Greeks and wine in Jewish and Christian ceremonies (Crocq, 2007). Opium and marijuana were widely used to treat several diseases: the earliest recorded use of cannabis is approximately 2700 BC when the "father of Chinese medicine" described the use of cannabis to treat several conditions (Childers and Breivogel, 1998), and opium was first mentioned in the ninth century BC in Homer's Odyssey as being able to treat a wide variety of diseases. In addition to opium and marijuana, tobacco also had an important medical use: traces of nicotine were found in children and adult hair samples from Nubian burial sites, indicating that plants containing nicotine may have been used as medical stimulants (Baez et al., 2000), and in 1492, tobacco was imported from San Salvador by Columbus to Europe to cure almost every pathological condition.

A third parallel and dominant pattern of use of the psychoactive substances was a regular consumption-based or socially accepted recreational consumption. Alcohol is probably the best example as its common recreational use since the beginning of history is well documented. During prehistoric times, as soon as humans realized that drinking the juices of fruits that had been exposed to airborne yeast produced pleasant and euphoric feelings, they began the production and cultivation of wine and beer: the oldest seeds of cultivated vines were found in Georgia (estimated 7000−5000 BC), and in ancient Mesopotamia (BCE 3000), beer was produced by the cultivation of wheat and barley. Marijuana was also intensively used in China, Central Asia, India, in Islamic culture, the Middle East, and Africa and was cultivated for psychoactive purposes in the Gobi desert about 2700 years ago (Russo et al., 2008). Opium and marijuana were used as primary social drugs, to relax and pass time by a wide range of cultures, eg, Romans, Indians, Assyrians, and Egyptians. Tobacco was similarly used for socialization in Europa. An evidence of recreational coca leaf chewing comes from chemical analysis of ancient hair samples from Chilean mummies dated 2000 BC−AD 1500, where the presence of the cocaine metabolite benzoylecgonine was detected (Cartmell et al., 1991).

Under these well-established cultural patterns, where the use of drugs as a vehicle to alter mood and behavior was socially accepted, abnormal patterns of consumption were almost absent as evidenced from few anecdotal descriptions. As an example, the earliest description of alcohol abuse is found in the Hebrew/Christian Bible, where in Genesis Chapter 9 verses 20−23, the Semite Patriarch Noah is described as becoming drunken, dishevelled, naked, and filthy from overindulgence in wine. Aristotle also recorded the effects of alcohol withdrawal and advised that drinking during pregnancy could be injurious, and the Roman physician Celsius held that dependence on intoxicating drink was a disease (O'Brien, 1980).

Addictive Drugs in Modern Times: Toward a Scientific Definition of Addiction

In sharp contrast to the prehistoric scenario described, in the 18th century, another picture raised: while only a few substances "survived" and retained the cultural uses (like some tribes from Australia, Amazon, Kalahari Desert, or Bolivian highlands), many other substances sifted to a non-socially accepted pattern of abuse and dependence. Why did those "controlled" behavioral patterns, which persisted across such a long period of time and virtually all cultures, change? Psychological and environmental variables

occurring during the 18th century played a crucial role in such a dramatic change in the behavior toward psychoactive drugs. More importantly, the recognition of this new and pathological use led to an explosion in drug research that culminated in the development of the science of addiction (Fig. 31.1).

The first variable was of a psychological nature. That is, although the primary motivation to use psychoactive drugs continued to be the alteration in mood and thinking, those substances started to be used to experience pleasure (regardless of any controlled or conventional environmental conditions). In another words, drugs were now used for illicit pleasures. The logical consequence of this behavior was a rapid increase in the consumption of drugs, which also extended to a wide diversity of groups. As a result, the first attempt to make those drugs illegal came with the Harrison Act in United States after the World War I, and the use became restricted to certain outsider groups. This situation continued escalating, and after World War II, consumption of those drugs became much more widespread for larger groups and for age of initiation.

A second variable that impacted the cultural history of drugs use was new advances in chemistry that made it possible to develop methods of purification, distillation, and isolation of drugs. As a result, the psychoactive properties of the existing drugs were increased, and the synthesis of new and more potent substances developed. Cocaine best represents this scenario: its isolation from the coca leaves in 1884 first spread its medical use as an anesthetic from pharmaceutical companies in Europe and the United States, and it later became a trendy stimulant in the upper classes. Its popularity was increased even more

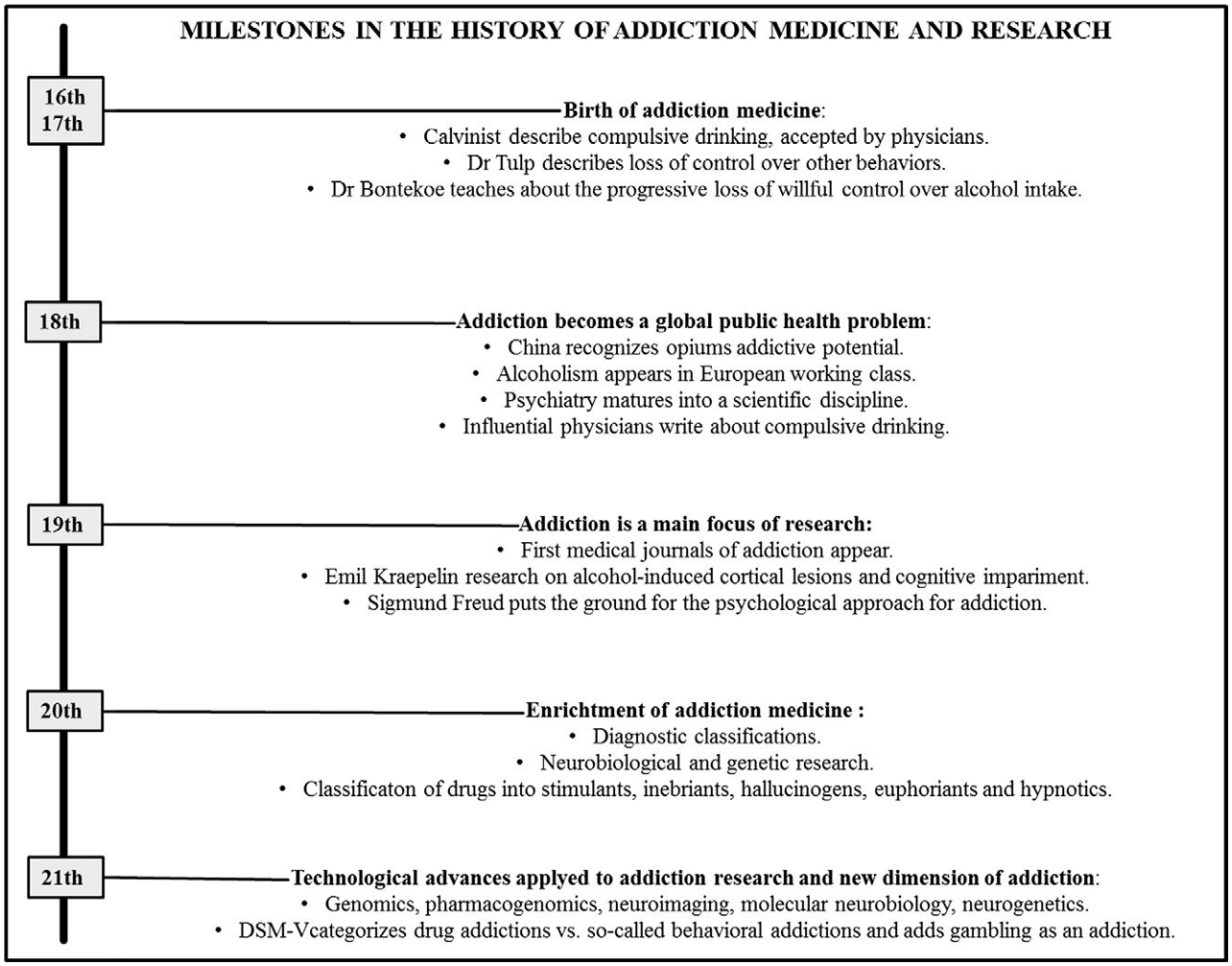

FIGURE 31.1 Milestones in the history of addiction medicine and research. The birth of addiction medicine in modern times is sometimes credited to Calvinist theologians who offered explanations for the phenomenon of compulsive drinking. With the colonial era, industrial revolution, and international trade, addiction became a global public health problem. The recognition of a pathological use of addictive drugs led to an explosion in research that culminated in the development of the science of addiction. The 21st century is characterized by the use of new technologies applied to addiction research and a new conceptualization of addiction disorder in the DSM-V.

by the psychiatrist Sigmund Freud, as well as by being the main ingredient in several products, like Coca-Cola, "a drink of intellect and moderation." Regarding the development of synthetic drugs, barbiturates, amphetamine, or heroin are the best examples: initially developed as medicines, they rapidly became associated with abuse.

In parallel, a third variable that strongly impacted and favored this new pattern of illicit drug use was the migrations of laborers from India or China to Europe and the United States who introduced cannabis and smoking opium to these lands.

The impact of these three variables was so strong that from the 19th century on a pathological use of these drugs was recognized, was defined as a disease, and was included in the medical community as becoming a public health problem. In this context, it is worth mentioning the epidemics explosion, such as the methamphetamine in Japan in the 1950s, cocaine in the United States in the 1980s, and crack cocaine of the 1990s. At this point, the urgent need for a definition and more knowledge about this disease lead to an explosion of research in neuroscience: the science of addiction appeared.

The Root of the Scientific Definition of Addiction

From 1956, when the American medical association declared that alcoholism is a disease, till now, research in the neuroscience field has been continuously developing the definition of addiction (Table 31.1). Now, addiction can be best defined as a behavioral syndrome, characterized by compulsive drug seeking with repeated relapses into drug use. More in detail, drug addiction or substance dependence (American Psychiatric Association, 1994) is a chronically relapsing disorder that is characterized by (1) compulsion to seek and take the drug, (2) loss of control in limiting intake, and (3) emergence of a negative emotional state, like anxiety or irritability, when access to the drug is prevented (defined as dependence). Addiction is further conceptualized as a progression from impulsivity to compulsivity, it and includes three stages: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation (Koob and Le Moal, 1997). Some modern views of addiction have focused the attention on three types of drug use (namely occasional, controlled, or social), abuse or harmful use, and addiction. In this regard, is important to note that other phenomena, such as physical dependence and withdrawal, have to be strictly separated from addictive behavior, as an individual can be physically dependent on a drug without being addicted to it and vice versa (Spanagel and Heilig, 2005).

The diagnostic criteria for addiction are described in the recently updated DSM-V and in the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10). The criteria outlined by both manuals are similar, and the number of criteria might vary with the severity of the addiction, the stage of the addiction process, and the drug in question (Chung and Martin, 2001). A well-accepted model illustrating the different stages of addiction was developed by Koob and Le Moal (2005). This model proposes that drug taking invariably begins with social drug taking and acute reinforcement, that often, but not exclusively, may move in a pattern of use from escalating compulsive use to dependence, withdrawal, and protracted abstinence. During withdrawal and protracted abstinence, relapse to compulsive use is likely to occur with a repeat of the cycle. Genetic factors, environmental factors, stress, and conditioning or learning all contribute to the vulnerability to enter the cycle of abuse/dependence and relapse within the cycle.

From a social psychology level, a self-regulation failure (loss of control) has been proposed as the root of a major social pathology in present times (Baumeister et al., 1994). At a neurobiological and behavioral level, such self-regulation failure is reflected in deficits in information processing, attention, planning, reasoning, self-monitoring, or inhibition (Giancola et al., 1996). From this view, the progression to develop addiction across the different stages described earlier might include crucial self-regulation elements, similar to other pathological behaviors, such as binge eating. Those failures in self-regulation in the context

TABLE 31.1 Development on the Scientific Definition of Addiction

Concept added to addiction definition	References
Romans: not linked to substance use; "addictus" was a term applied to a person in a legal slave-like condition	Smith (1898)
DSM-III-R: substance use	American Psychiatric Association (1994)
Compulsive drug use	O'Brien et al. (2006)
DSM-IV: substance-related disorders	American Psychiatric Association (1994)
DSM-V: substance-related and addictive disorders	American Psychiatric Association (2013)

of drug use might lead to the development of an addictive behavior. Particularly, the failure in self-regulation is reflected in strength deficits, failure to establish standards or conflict in standards, and attention failures, as well as misregulation (misdirected attempts to self-regulate) contributing to the development of addiction-like patterns of behavior (Koob and Le Moal, 2005). Repeated self-regulation failures might lead to an emotional distress that would start a cycle of repeated failures to self-regulate, resulting in spiraling distress (Baumeister et al., 1994). This process may lead to either initiating or preventing the exit from the addiction cycle.

Although this view of addiction has been predominant across the 20th and 21st centuries, advances in neuroscience, and clinical and public health have added new aspects and expanded the scientific definition of addiction. Illustrating this, the term addiction has been also applied to a range of problematic behaviors such as pathological gambling, pathological internet use, and binge eating to mention only a few. This is reflected in the new DSM-V, which marks the first significant revision of the publication since the DSM-IV in 1994 (American Psychiatric Association, 1994), and the upcoming ICD 11th edition (ICD-11). Thus, the new psychiatric classification system DSM-V has for the first time categorized drug addictions vs. so-called behavioral addictions. This marks a milestone in psychiatry. Thus, the addition of gambling disorder as a behavioral addiction together with the replacement of abuse and dependence criteria with a single substance use disorder entity in the new DSM-V might point toward a new dimension of addiction. This new conceptualization may open a new era of addiction in science where other potential behavioral addictions like sexual, internet, shopping, sports, or eating might be (scientifically) defined. Supporting this idea, emerging neurobiological and clinical data collectively suggest that overlaps exist between food and drug addiction. In fact, the behavioral phenotypes associated with obesity resemble those of drug addiction: compulsive overconsumption, difficulty controlling the intake of food, and the emergence of negative emotional states. Still, although the idea that the development of an addiction to food (ie, overeating) may be the cause of the increasing prevalence of obesity, the term "food addiction" still remains a subject of debate.

ROOTS OF REINFORCEMENT AND MOTIVATION IN ADDICTION

The psychological constructs through which drugs modify gradually behavior during the transition to addiction depend on learning and the formation of long-lasting conditioned associations, and they include multiple motivational mechanisms. In the following sections, I will describe first the different theories or models explaining the psychological mechanisms underlying the process of addiction and will give an overview of the neuroanatomical substrate mediating those processes, the so-called brain reward system. Finally, I will describe the particular motivational and psychological alterations underlying dependence, craving and relapse, core features of addiction.

Psychological and Motivational Mechanisms in Addiction: Reward Dysregulation

A common view for many scientific theories of addiction is that changes in relative reward value underlie the addictive process; in fact, it is known that in drug addicts, drugs are more powerful than natural rewards. Thus, evidence from subjective measures together with some alterations in the brain reward system found in drug addicts (Volkow et al., 1999) have led to the conceptualization of addiction as a reward deficiency syndrome (Blum et al., 1996). This concept of reduced reward sensitivity characterizing addiction has become a central pillar from different approaches or theories aiming to explain the motivational/psychological mechanisms involved in the addiction process, described as follows (Table 31.2).

The first is the *counter-adaptation opponent-process and allostasis model*. This theory, first developed by Solomon and Corbit (1974), proposes that the initial acute effect of the drug is opposed or counteracted by homeostatic changes in systems that mediate primary drug effects, resulting in a reduction of the intensity of the hedonic feelings experienced initially (Solomon and Corbit, 1974; Poulos and Cappell, 1991). The current view of this theory was originated by Koob and Le Moal, and it states that prolonged drug use can lead to a general state of anhedonia, and only very powerful rewards can overcome such a state. Thus, the positive effect ("process a") from drug-taking produces automatically a counteracting, opponent "process b" to maintain homeostasis. After experience, the "b process" occurs more readily and in greater magnitude, resulting in an attenuation of the "a process," or the positive effects of drugs, ultimately becoming the homeostatic set point. More importantly, this theory predicts that the decreased sensitivity to the drug is associated with increased motivation to obtain it. A similar shift in the homeostatic level of control is hypothesized for signs of withdrawal and precipitated abstinence in chronically dependent subjects (Koob and Le Moal, 2005). It has been proposed that these opponent processes (ie, drug-induced state of anhedonia) represent one of the major motivations for compulsivity in drug taking in the form of a motivational withdrawal syndrome (Koob and Volokw, 2010). Thus, manifestation of a withdrawal syndrome after removal of chronic drug administration, either acute or protracted, is defined in terms of motivational aspects of

TABLE 31.2 Psychological Processes and Constructs Associated to Addiction

Term	Definition
Motivation	Theoretical construct used to explain behavior. It represents the reasons for people's actions, desires, and needs. Motivation can also be defined as one's direction to behavior or what causes a person to want to repeat a behavior and vice versa.
Reward	Stimuli that the brain interprets as intrinsically positive or as something to be approached.
Reinforcer	Stimuli that increase the probability of repeating behaviors paired with them.
Positive reinforcement	Process by which the presentation of a stimulus increases the probability of a response.
Negative reinforcement	Process by which the removal of a (usually aversive) stimulus increases the probability of a response.
Compulsivity	Elements of behavior that result in perseveration in responding in the face of adverse consequences, perseveration in responding in the face of incorrect responses in choice situations, or persistent re-initiation of habitual acts.
Impulsivity	Predisposition toward rapid, unplanned reactions to either internal or external stimuli without regard for negative consequences.
Associative learning	Process by which an association between two stimuli or a behavior and a stimulus is learned. The two forms of associative learning are classical and operant conditioning.
Conditioning	A form of learning in which (1) one stimulus comes to signal the occurrence of a second stimulus (Pavlovian) or (2) behavior is modified by its consequences (instrumental conditioning).
Habit	A more or less fixed way of thinking, willing, or feeling acquired through previous repetition of a mental experience.

dependence such as the emergence of a negative emotional state (eg, dysphoria, anxiety, irritability) when access to the drug is prevented (Koob and Le Moal, 2001), rather than on the physical signs of dependence, which tend to be of short duration (Koob and Volkow, 2010).

In the *incentive sensitization theory*, the motivational changes characteristic of the addictive behavior are conceptualized from a reward dysregulation perspective developed by Robinson and Berridge (1993, 2000). This theory proposes that repeated drug use sensitizes neuronal circuits that mediate psychostimulant motor effects (behavioral sensitization), drug reward (incentive motivation), and the attribution of incentive salience to reward-associated environmental cues (conditioned reinforcement, maladaptive associative learning). Importantly, this theory clearly dissociates between drug "wanting," defined as the motivation to take the drug, and drug "liking," defined as the unconscious hedonic experience derived from consuming the drug, and it proposes that the "wanting" but not the "liking" is critical in the development and maintenance of an addictive behavior. Thus, a shift in an incentive salience state, described as "wanting" linked to compulsive use, as opposed to "liking" linked to hedonic responses, was hypothesized to be progressively increased by repeated exposure to drugs of abuse (Robinson and Berridge, 1993). This psychological process of incentive salience is responsible for drug-seeking and drug-taking behavior (Robinson and Berridge, 2003). First, once sensitized, this incentive salience process produces compulsive patterns of drug use; second, through associative learning processes, the enhanced incentive value becomes oriented specifically toward drug-related stimuli, leading to escalating compulsion for seeking and taking drugs. Supporting this assumption, clinical observations from addicts to psychostimulants show unusual focus on drug seeking, which originates from the facilitation of conditioned reinforcement and drug seeking (Robbins, 1976; Hill, 1970). In this way, drug seeking is controlled by a succession of drug-associated discriminative stimuli that can also function as conditioned reinforcers when presented as a consequence of instrumental responses (Everitt et al., 2008). In addition, a compulsive escalation of drug taking and seeking may also result from an enhanced incentive salience state, oriented specifically toward drug-related stimuli by means of associative learning processes (Hyman et al., 2006; Kalivas and Volkow, 2005). Interestingly, similar to the opponent process theory, Robinson and Berridge proposed that the affective experience of the drug (thus the liking) decreases after repeated use.

A third view comes from the *transition to habit* theory of Everitt and Robbins (2005; Everitt et al., 2008). Here, a switch from a reward-sensitive behavior to a habit-based behavior is proposed to underlie decreased reward sensitivity. That is, while initially drug seeking is triggered by a mental representation of the reward (Tiffany, 1990; Everitt et al., 2001; Dickinson et al., 2002), after chronic use, this

conscious representation is no longer needed, and the seeking behavior will be triggered by a stimulus–response habit; consequently, the habit (and not the affective reward response) will be critical in maintaining the addictive behavior. From this perspective, it is proposed that an initial drug seeking is goal-directed; following extended use, it comes under habitual stimulus–response control and so does the acquired natural reward seeking. Then, the behavioral repertoire comes to be dominated by stimulus–response habits. The main feature of habits, opposite of goal-directed actions, is that they are not guided by the motivational value of the reward, and they are directly triggered by conditioned stimuli without any recruitment of higher cognitive processes, such as intention or decision-making (Belin et al., 2013). Illustrating this, an imaging study has shown activation of habit-related brain areas when craving is provoked by cues in cocaine users (Childress et al., 1999). In humans, little evidence exists of habit learning controlling drug-seeking behavior. These studies have shown that smoking deprivation increases motivation for tobacco smoke in instrumental and choice measures (Epstein et al., 1991; Madden and Bickel, 1999; Perkins et al., 1994, 1996; Rusted et al., 1998; Willner et al., 1995). More recently, a comparable effect of no contingent alcohol exposure on habitual control has been demonstrated (Hogarth et al., 2012). This study showed that alcohol attenuated goal-directed control over chocolate choice in the extinction test, suggesting accelerated habit learning.

A last theory comes from the *impulsivity models*, which propose that prolonged drug intake affects impulse control mechanisms that may lead to addictive behaviors (for a review see Stephens et al., 2010). The rationale of this theory comes from three different sources: First, impulsive control disorders might be thought of as a (non-substance) behavioral addiction (Grant, 2008); second, early work already pointed out an association between alcohol use and impulsivity (Cloninger, 1987), and studies with nonhuman primates have also shown increased impulsivity and alcohol consumption (Higley et al., 1996a,b; Mehlman et al., 1994), and third, many behavioral and neurobiological studies have consistently shown frontal cortical dysfunction in human drug users, a brain region directly involved in impulse control. In this sense, crucial studies have shown changes in regional cerebral blood flow of cocaine users (Volkow et al., 1993), structural volume (Liu et al., 1998), as well as D2 dopamine receptor binding (Volkow et al., 1993) in prefrontal regions. Importantly, some of those findings have been replicated in animal studies (Stephens et al., 2010). Thus from this view, rather than the motivational systems (ie, brain reward system), the frontostriatal inhibitory mechanisms play a dominant role in the reward devaluation and therefore addiction.

In conclusion, the motivational/psychological view of addiction provided by different theories indicates the complexity of alterations in reward value and their impact on drug addiction. Those different motivational processes lead to a reward dysregulation and ultimately drive impulse control disorders and compulsive disorders characteristic of the addictive phenotype.

The Brain Reward System: Substrate for Neuroadaptations in Addiction

Rewards (Table 31.2) have their origin in drinking, eating, and reproduction, and the brain reward system mediates motivational responses related to these natural rewards. Consequently, the reward system provides the anatomical substrate for emotions and motivated behavior, including the circuitry for reward-related events. Since drugs of abuse are also rewarding and reinforcing, they also act through the reward system, this system being the substrate of the changes in the motivational aspects described earlier. Indeed, already in 1979, Goldstein made the claim that heroin and other narcotics worked on a bundle of neurons deep in the brain called the mesolimbic dopaminergic pathway (Hokfelt et al., 1979).

The reward system consists of a set of interconnected forebrain structures often called brain reward pathways. In a simplified way, these structures include the nucleus accumbens (NAc), the basal forebrain, and regions of the prefrontal cortex (Fig. 31.2), being most of the pathways which connect these structures within the reward system glutamatergic interneurons, GABAergic medium spiny neurons, and dopaminergic projection neurons. It appears that both addictive drugs and natural rewards are rewarding and reinforcing because they act within this system to enhance dopamine release in the NAc or related structures. In particular, a group of neurons known as the mesolimbic dopamine pathway, which connect to the NAc, along with the associated GABAergic medium spiny neurons in the NAc, is a critical component of the reward system that is directly involved in the immediate perception of reward (Kalivas and Nakamura, 1999).

Natural and drug rewards impact the reward system in different ways; subsequently, compared with the normal brain, the addicted brain programs behavior differently. First, a natural activation of the reward pathway is triggered by sensory cues that are produced by natural reinforcers (like food, water, or sex); in contrast, the activation of this same circuitry by addictive drugs is triggered by chemical means, circumventing the need for evolutionary useful behaviors (Schultz, 2000). Accordingly, the powerful control over behavior exerted by addictive drugs may have a first origin from the brains inability to distinguish between the activation of reward circuitry by drugs and natural activation of the same circuitry by useful and necessary

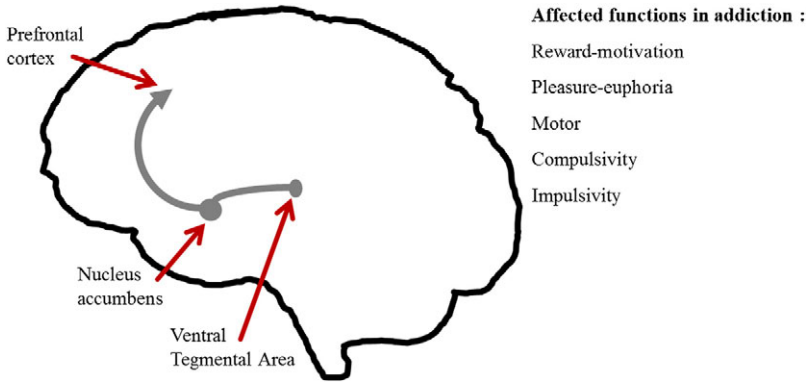

FIGURE 31.2 Schematic representation of the brain reward system. The reward system consists on a set of interconnected forebrain structures including the NAc, ventral tegmental area, the basal forebrain, and regions of the prefrontal cortex (PFC). These structures are interconnected within the reward system by glutamatergic interneurons, GABAergic medium spiny neurons, and dopaminergic projection neurons (shown in the figure). The reward system provides the anatomical substrate for drug-induced alterations in emotions and motivated behaviors.

behaviors for survival and reproduction. Indeed, the chemical activation of the reward system by drugs of abuse produces not only extreme states of euphoria (that may motivate repeated drug use) but also underlies the extreme adaptations in motivational behavior. Moreover, it is believed that repeated exposure to drugs induces cellular and molecular changes within the reward pathway, which in turn cause alterations in reinforcement, motivational mechanisms, and memory systems mechanisms that contribute to sustain addiction over long periods of time (Nestler and Aghajanian, 1997). These changes ultimately usurp normal learning mechanisms to shift neurocircuitry to associations or a form of habit learning that persists in the face of significant adverse consequences (Everitt and Wolf, 2002; Hyman et al., 2006).

The functional consequences of chronic, long-term exposure to addictive drugs believed to underlie addiction are mainly the development of tolerance, sensitization, and dependence. Tolerance is a pharmacological term to describe when a subject's reaction to a specific drug and concentration of the drug is reduced followed repeated use, requiring an increased dose to achieve the desired effect. Behavioral tolerance occurs with the use of certain psychoactive drugs, where tolerance to a behavioral effect of a drug, such as increased motor activity by methamphetamine, occurs with repeated use. This form of tolerance is a more important mechanism in terms of its contribution to addictive behavior. The opposite phenomenon to tolerance is the development of sensitization, also known as reverse tolerance. Sensitization to drugs occurs when repeated administration of the same drug dose elicits escalating effects. Eric Kandel, Nobel Prize in Physiology or Medicine for his research in neuronal learning processes, was one of the first to study the neural basis of sensitization, conducting experiments in the 1960 and 1970s on the gill withdrawal reflex of the sea slug *Aplysia*. He observed that after sensitization, a light touch to the siphon alone produced a strong gill withdrawal response, and this sensitization effect lasted for several days (Squire and Kandel, 2009). Last, dependence develops in response to repeated drug administration and is linked to withdrawal. It has both a somatic component, manifested by physical symptoms that develop when the drug use ceases (ie, during withdrawal), and an emotional-motivational component, manifested by dysphoria and anhedonic symptoms that occur when a drug is discontinued.

Neuropsychological Adaptations of Dependence, Craving and Relapse in Humans

As aforementioned, addiction represents sequential neuronal, motivational/affective, and behavioral adaptations. Consequently, the initial action of consuming an addictive drug turns impulsive after repeated use, then compulsive, and eventually may become chronic and relapsing. According to human studies, this process of transition involves progressive new programming of neural circuits that mediate reward and motivation, memory, conditioning, and habituation processes, executive function and inhibitory control, interoception and self-awareness, and stress reactivity (Koob and Volkow, 2010).

In most cases, the driving force for initiating the abuse is experiencing their hedonic properties. Nevertheless, another driving force may be found in the reinforcing effects derived from conforming social groups, with the eventual subsequent transfer of motivation to taking the drug for its reinforcing effects. In another cases, a drug may be consumed because of its therapeutic properties (ie, opiate analgesics for pain or amphetamine for attention-deficit hyperactivity disorder). As already mentioned, it is largely accepted that this first reinforcing or euphoric effect results from a large increase in dopamine release in the reward system (including the NAc). Indeed, brain imaging has confirmed that drug-induced increases in dopamine in the striatum (a part of the reward system where the NAc is located) are associated with subjective descriptors of

reward (eg, pleasure, high, euphoria; Volkow et al., 1996). Another neurobehavioral aspect that adapts during addiction is expectation. As the drug consumption becomes chronic, the expectation of the drug's effects significantly influences the rewarding responses to drugs, such that the behavioral (together with regional brain activation) response to the drug tends to be more intense when a rewarding drug is expected compared with when the same drug is received unexpectedly (Volkow et al., 2003). Surprisingly, the desire for a drug is clearly different from the initial rewarding effect, and in many cases the chronic intake of the drug continues despite the fact that the drug has lost some of its associated euphoric effects (as a result of tolerance).

When drug intake is discontinued in chronic drug users, different physical withdrawal syndromes are triggered that depend on the drug per se (ie, psychostimulants, alcohol, or opiates) and the chronicity and frequency of its abuse. Despite this, all drugs of abuse (when the intake is interrupted) include a common motivational withdrawal syndrome characterized by dysphoria, irritability, emotional distress, and sleep disturbances that persist even after protracted withdrawal. Although both acute and protracted withdrawal syndromes contribute to relapse, the neuropsychological response of acute withdrawal is distinct from protracted or motivational withdrawal (once the symptoms of acute withdrawal have subsided) as the latest is intensified with repeated withdrawals. In addition, imaging studies have documented hypofunction in dopamine pathways during protracted withdrawal, which may contribute to the anhedonia or decreased sensitivity to rewarding stimuli (including drugs) and lack of motivation reported by drug-addicted subjects (Martinez et al., 2004, 2005; Volkow et al., 1997, 2007). Another neuropsychological response that is altered during protracted withdrawal is drug-related conditioned association processes; imaging studies have documented that in contrast to the decreased sensitivity to rewards, enhanced sensitivity to conditioned cues also occurs. Abstinence from smoking, for example, can dramatically potentiate neural responses to smoking-related cues (McClernon et al., 2009). The intensification of these conditioned responses is critically important in sustaining the cycle of abstinence and relapse that characterizes substance use disorders (Childress et al., 1988). Last, imaging studies have shown that drug abusers tested during protracted detoxification show evidence of disrupted activity of frontal regions, which is hypothesized to underlie their impaired inhibitory control and impulsivity and contribute to relapse (Koob and Volkow, 2010).

As a result of this enhanced sensitivity to conditioned cues including emotional states, a latent preoccupation/anticipation (craving) stage arises, which is characterized by an increase in drug desire or craving. Although craving per se often does not correlate well with the relapse, stress does so, and enhanced sensitivity to stressors is characteristic during craving. Moreover, stress is a powerful trigger of relapse to drug-taking behaviors through the activation of brain circuits involved in reward processing and in the attentional and mnemonic bias for drug use reminders (Duncan et al., 2007). Indeed, the chronic relapse phenomenon is one of the most challenging problems in treating addiction, as addicted subjects are likely to return to compulsive drug taking long after experiencing acute withdrawal symptoms (Langleben et al., 2008). Besides, addicted humans (to cocaine) show impaired performance in tasks involving attention, cognitive flexibility, and delayed reward discounting, as well as spatial, verbal, and recognition memory impairment, deficits that can also predict poor treatment outcomes (Aharonovich et al., 2006; Bolla et al., 2003). In this regard, a gradual reorganization of reward and memory circuits occurring across the chronic drug abuse is proposed to be crucial.

In conclusion, the roots of reinforcement and motivation in addiction can be conceptualized by different theories explaining the complexity of alterations in reward value and their impact on drug addiction. The anatomical substrate of those motivational processes leading to reward dysregulation includes the brain reward system that will be differently affected during dependence, craving, and relapse.

DISSECTING ADDICTIVE BEHAVIOR: APPROACHES TO MEASURE REWARD AND ADDICTIVE PHENOTYPES IN HUMANS AND ANIMALS

To have a better understanding of the complex phenomenon of addiction, two aspects are fundamental: first, it is of crucial importance to elucidate how rewards and reinforcement processes impact on the addictive behavior, and second, which are the relevant behavioral hallmarks of addiction. To that end, first I will describe different approaches used in the laboratory to measure reward in humans. Next, I will describe preclinical and basic research with animals aiming to isolate and analyze the complexity of addiction, by studying drug-induced reinforcement processes and mimicking human addictive phenotypes.

Measuring Reward in Humans

The "gold standard" test for assessing the initial abuse liability of a novel drug is the classic acute dose-effect comparison study (Griffiths et al., 2003). This test is usually performed in volunteers with histories of drug abuse, and it is appropriate for predicting the likelihood of abuse by drug abusers. In addition, it provides crucial information about potential abuse risk of marketing of a novel compound as well as about some adverse consequences of its

recreational abuse. Most importantly, the dose-effect comparison test is also helpful in establishing parameters for subsequent studies using other methods, like those described subsequently (Stephens et al., 2010).

Another method used to measure reward and addiction liability in humans is the self-report. Usually, self-reports are developed in the laboratory to measure the rewarding properties of a given drug that is being abused. Although it is a good and direct indicator of a drug's rewarding value, an important limitation of using self-report measures is that substance-dependent individuals may have low insight (or consciousness) into their motivations and misrepresent their thoughts and feelings, or their reports may be biased due to social desirability (Marhe et al., 2014). Besides this, an additional limitation comes from the multifaceted aspect of the pleasurable feelings reported that may have both components of positively reinforcing drug effects (ie, euphoria or high) as well as negatively reinforcing effects (ie, relaxation due to relief from tension and craving). Exemplifying this with alcohol, the subjective response to alcohol includes euphorigenic, stimulating, and anxiolytic/sedative components, and it is not clear which of those components is associated to abuse liability. A "differentiator model" has been proposed, which suggests that rapid dynamic changes (acute tolerance) to some, but not other, components may in fact drive the addictive process (Newlin and Thomson, 1990).

Drugs effects can also be examined through the use of subject ratings of estimates of street value, as a measure of the rewarding properties of a drug given in the laboratory (Roache and Griffiths, 1985), and it is well established that they can predict abuse liability and diversion (Griffiths et al., 2003). That is, it is hypothesized that drugs reported to have high monetary value also have high rewarding properties. In fact, many studies have evidenced a constant ranking of the street value between several drugs, places, and times, which strongly proposes the estimates value as a useful measure of abuse liability. Still, since the rating can vary across cultures and over time, they may only be useful within a single study and when current street values are taken into account (Foltin and Fischman, 1991).

Another method is the self-administration, which measures operant responding, in which participants make a behavioral response (such as pressing a spacebar) to receive drug. Laboratory self-administration studies have focused on heroin, cocaine, cannabis, amphetamines, nicotine, and benzodiazepines (Comer et al., 2008; Haney, 2009; Haney and Spealman, 2008; Justinova et al., 2005; Koob, 2009; Panlilio and Goldberg, 2007) more frequently than on alcohol (Zimmermann et al., 2009), being the frequency availability for each particular drug similar to the pattern by which the drug is normally abused. Self-administration sessions in the laboratory provide measures of reinforcement and ratings of drug and mood effects, which provide information on drug craving, and the subjective experience of the drug; volunteers may also be studied under the withdrawal syndrome, or they may be allowed to self-administer the drug to prevent the onset of withdrawal symptoms. One main advantage in controlled self-administration studies is that meaningful behavioral data can be obtained in a relatively small number of individuals. Results obtained by several studies using cocaine, heroin, or cannabis self-administration support the importance of this model in terms of predicting medication effects. Therefore, these studies contribute to our understanding of the variables maintaining cocaine, marijuana, and heroin intake, and they are important in guiding the development of more effective treatment and prevention programs (Haney, 2009). A particularly interesting feature of this method consists of its great homology with animal self-administration models (see later section) and therefore can be potentially used for translational research studies. However, some differences must be considered before comparing them. A major difference relies on the human insight into the nature of the experiments and the ability to anticipate the outcome of prolonged sequences of behavior.

A more objective measure for evaluating the rewarding properties of drugs is the choice procedure. Here, under controlled laboratory settings, the subjects are able to request an aliquot of the drug when required, and use is noted (Griffiths et al., 1986). In the verbal variant of the procedure, individuals are given samples doses of both the drug and placebo and required to choose one by verbal report (de Wit and Chutuape, 1993), thus providing measures of the rewarding properties of both substances. Besides providing measures of the rewarding properties of both the drug and the placebo, these procedures also indicate the preference of the drug over placebo by means of self-reports of linking or over a monetary reward (Fillmore and Rush, 2001). As for the self-administration procedures, the choice method can also be directly compared to drug-conditioning procedures with laboratory animals (see later section) and, therefore, might also be useful in translational studies.

A more recent approach comes from the rewarding behavioral economic perspective. In general, behavioral economics provides a framework to understand when and how people make errors, and a key concept in behavioral economics focuses on how delayed rewards are discounted and how there is deviation from the rational-choice paradigm (Heshmat, 2015). A main advantage of this approach is the direct comparison between qualitatively different reinforcers (drugs or drug doses) and the assessment of interactions between them. This is supported by several studies showing that drug-dependent subjects tended to be less sensitive to changes in price of their drug of choice, in comparison to other drugs of abuse (Jacobs and Bickel, 1999). A limitation of this perspective lies on the fact that it

does not assume that behavior is rational and therefore disconnects descriptive models (characterizations of actual behavior) from normative models (characterizations of optimal behavior) (Monteroso et al., 2012). Although this perspective has not been deeply developed so far in the addiction research field, the delay-discounting procedure has recently become a focus of interest for modeling differences in impulsivity in preclinical research (Wilhelm and Mitchell, 2008).

Among the measurements of reward in humans, "craving" is most probably the one that has attracted more attention as a core component of drug abuse. Indeed, it has been suggested that many of the symptoms of craving in the dependent individual are similar to the thought patterns and behaviors of persons with obsessive-compulsive disorder, including recurrent and persistent thoughts about the drug and the inability of the individual to resist these thoughts and a compulsive drive to consume the drug and loss of control over that drive (Modell et al., 1992). According to this, the main component of craving might not only be the desire to take the drug but also a measure of incentive, and the current theories differ on that. In this regard, the relevance or weight of craving in addiction is a matter of debate, and it ranges from a denial that craving plays any role (Tiffany, 1990) to craving either emerging from the subjective experience to take drug, or being synonymous to motivation, being triggered by signals of drug availability (Robinson and Berridge, 1993; Stewart et al., 1984). A theory that might reconcile the different aspects of craving and their role in addiction might be the incentive sensitization hypothesis proposed by Robinson and Berridge (Robinson and Berridge, 2003). Thus, this theory proposed two separate aspects of reward: incentive motivation (defined as the desire to obtain the reward; "wanting") and reward derived from consumption (defined as hedonic value, or liking). Consequently, craving would reflect the "wanting" aspect, and other affective responses index "liking." Thus, the "liking" of the drug may not be predictive for its self-administration, or for it to be chosen over an alternative, non-rewarding option (Stephens et al., 2010). In addition, indirect measurement of craving like attentional biases or physiological responses to cues associated with drug experience has also been proposed (Carter and Tiffany, 1999; Tiffany, 1990). Such measures, however, show a poor relationship to subjective measurements of craving. It is worth to point out here that preclinical and basic research with rodents has developed methods to measure craving that are consistent with the incentive theory addiction (see later section).

Modeling relapse situations and compulsive drug seeking in laboratory settings remains a challenge in the field of human research. A key challenge is the ecological relevance of the method used for provocation, especially when the participants are under psychopathological conditions (Brady and Sinha, 2005). The use of standardized provocation methods mask individual differences in relapse situations, making it not possible to capture drug-related particular associations involved in the motivational processes that lead to craving or relapse (McKay et al., 1996). Another challenge is to address alterations in stress responses. This is particularly important, as relapse often involves drug-related emotional or stressful stimuli, triggering or activating stress pathways. To overcome these caveats, there has been an effort in the last years to better capture the relapse in the laboratory and to develop a valid laboratory model. Sinha proposed four objectives to be achieved to develop a validated method to study relapse in alcoholics (Sinha, 2009). The method should do the following: reproduce a hallmark disease symptom (ie, craving) providing internal validity; provoke a particular disease symptom that, in turn, should be associated with the severity of alcoholism; be predictive of alcohol use behaviors and real-world clinical outcomes and be sensitive to intervention, improving, or worsening the disease. To improve the method, the studies by Sinha focused on the development of a relevant and ecological method that models relapse risk in real-world situations, therefore providing information about behavioral mechanisms of relapse vulnerability. In this regard, a key aspect of the method was to trigger two of the most common relapse situations, namely stressful and drug-related situations to make this method comparable to stress- and drug-related craving provocation. Another key aspect of the method was to add adequate within-group control conditions and/or between-group controls such as non-addicted healthy controls to control unspecific aspects of the experimental procedure.

In general, it is an obvious conclusion that addiction research in experimental human models is limited due to the technical and ethical aspects involved (the latter not discussed here). Therefore, human addiction is not reproducible within the laboratory settings. For that reason, the ultimate goal and challenge of measuring reward in humans is to model these laboratory human conditions in animals, as there is a continuous need to better understand what causes addiction and the neurobiological mechanisms underlying addictive disorders.

Measuring Addictive Phenotypes in Animals

In addition to the limitation of the human studies and considering the complexity of the addiction disorder that involves multiple environmental and genetic interactions (discussed later), the need for adequate behavioral animal paradigms to investigate the neurobiological mechanisms of addiction is of great importance. In this regard, a parallel progress done in the behavioral field during the previous

TABLE 31.3 Measurements of Reward and Drug Reinforcement in Human and Laboratory Animals

Human Method	Animal Method	Aspect Measured
Self-report		Rewarding Properties
Acute dose-effect	Operant self-administration	Reinforcement, Rewarding properties
Estimates of street value	Oral self-administration, CPP	Rewarding properties, Preference
Operant self-administration	Operant self-administration	Reinforcement
Choice procedure	CPP	Rewarding properties, Preference
Delay discounting	Operant self-administration	Reinforcement, Preference
Brain stimulation	Brain stimulation	Rewarding Properties

years, aiming to isolate and analyze the complexity of addiction, has resulted in the development of animal models highly sophisticated in studying drug-induced reinforcement processes and mimicking each particular phase of the addiction cycle (Table 31.3).

Before describing them (for a detailed description, see Sanchis-Segura and Spanagel, 2006), it is important to note that an animal model must be reliable and validated. Reliability refers to the consistency with which the variable under study can be measured and is achieved when after repeated measurements the between and within-subject variability is small. The most relevant concept in the validation of an animal model is the construct validity (Ebel, 1961). It refers to the explanatory power of the model, and the requirement that models meet the construct of functional equivalence, or how controlling variables influence the outcome in the model and the target disorder (Katz and Higgins, 2003). The face validity refers to the reproduction in the animals of the syndromes found in humans (McKinney, 1998). The predictive validity refers to the ability to lead to accurate predictions about the human phenomenon based on the response of the model. Most often, it refers to the ability of the model to identify pharmacological agents with potential therapeutic use in humans (McKinney, 1998).

Drug-Induced Reinforcement

It is considered that the reinforcing or rewarding effects of drugs are important in the initiation of the addiction cycle. The motivational properties of rewards are evaluated through consumption/preference-based measures; these include self-administration, conditioned place preference (CPP), and brain self-stimulation paradigms. Thus, drugs with positive reinforcing effects on those paradigms might also have a high abuse potential.

Self-administration-based methods are probably the most commonly employed models for measuring reward value in laboratory animals. In general, they can be classified in non-operant and operant methods. The non-operant procedures almost exclusively involve oral alcohol self-administration, mainly because of the obvious face and construct validity as models of human alcohol consumption. In particular, the initiation and maintenance of alcohol consumption, as well as the escalation of alcohol drinking (Rosenwasser et al., 2013; Linsenbardt and Boehm, 2014) and relapse-like drinking (Vengeliene et al., 2014), are successfully demonstrated by various voluntary free-choice alcohol drinking paradigms in the home cage. Regardless of the modifications of the drinking procedure, the experimental approach usually consists of monitoring the daily amount of alcohol consumed from a bottle containing an alcohol solution (5–40%) in the home cage and the choice between alcohol and water. In this procedure, the concentration of alcohol is critical and might influence the amount and pattern of intake in rodents. Indeed, because rodents have an innate aversion to alcohol taste, several procedures have been developed to overcome this and train the rodents to self-administer pharmacologically relevant amounts of alcohol. Such procedures include the presentation of ascending concentrations of ethanol and/or the addition of a sweet flavor agent (ie, sucrose or saccharine), the inclusion of a time period of forced exposure to ethanol, or a short period of water deprivation (usually no more than 20 h) before the alcohol bottle availability. Another important variable to consider when using the oral self-administration model is the rodent strain, as it is known that strains, particularly mice, differ in their intake and preference for alcohol (ie, low versus high alcohol drinking mice). Moreover, this aspect is particularly relevant when using genetically modified mouse models (for a review see Bilbao, 2013a). For the home cage drinking paradigms, simple alcohol intake and preference measures have been developed. The preference measure gives a general overview of drinking behavior and usually decreases with increasing alcohol concentrations, but it provides no information on the net alcohol intake. While the intake profiles are usually best described by ethanol intake in g/kg body weight per day, this

measure does not address the fact that a less concentrated alcohol solution takes longer time to ingest and therefore may have a different effect on the brain. Thus, the amount of accompanying water, as well as the time required to drink the amount of net alcohol, varies greatly in respect to the ethanol concentration. This should especially be taken into account in a multiple-concentration approach, ie, in free-choice drinking procedures from multiple bottles (with $\geq$3 bottles) containing water vs. different concentrations of ethanol solutions. For such a paradigm, the so-called "water-penalized net ethanol intake" measure has been developed (Pildaín et al., 2013). This measure provides the best stability for repeated baseline assessments and long-term experiments (Pildaín et al., 2013). Although all modifications of home cage free-choice alcohol drinking paradigms lead to an animal model with good face validity, these procedures are limited in the accuracy and timely resolution of the aforementioned measures of drinking behavior. This is a particular problem when animals drink small amounts (on a drinking occasion, a mouse usually drinks 10–20 μL) and evaporation and dropping of the bottles lead to errors in measurement. In addition, the manual measurements are a disruptive element for the animals that may affect drinking behavior. Furthermore, many of the experimental conditions in alcohol research require the determination of consumption patterns within hours or even minutes. Such experimental situations include assessing the onset of a pharmacological treatment or the effect of environmental manipulations like stress on alcohol drinking behavior (Peters et al., 2013; Spanagel et al., 2014b). To overcome these limitations, we recently have developed a fully automated, highly precise monitoring system for alcohol drinking in mice in the home cage that allows for detecting micro-drinking and circadian drinking patterns (Fig. 31.3, Eisenhardt et al., 2015b).

The operant or instrumental procedures of self-administration are conducted in the so-called operant or skinner boxes. In brief, they include levers or nose poking linked to the delivery of a reinforcer. As for the non-operant procedures, many approaches here are designed to overcome the sometimes aversive effects of initial exposure to drugs. Thus, similar to non-operant procedures, animals can be exposed initially to lower concentrations of the drug that will be slowly increased. A main advantage of this approach compared to the non-operant methods is that the effort to obtain the reward can be separately assessed from the pure consummatory response. In addition, control variables can be implemented into the schedule of reinforcement that will provide information about nonspecific motor responses by introducing a second, non-active lever or nose-poke (where its activation has no consequences). The most common schedule of reinforcement used in these studies is the fixed ratio, where the reinforcer is delivered every time that a preselected number of responses are completed. In these continuous schedules, animals will maintain a stable level of responding, and the rate of responding will increase as the dose unit will decrease and vice versa. In this regard, it has been suggested that manipulations that increase the self-administration rate resemble decreases in the unit dose, and they may be interpreted as decreases in the reinforcing potency of the drug (Caine et al., 1993). Another variation of these procedures is the second-order schedule. Here, the main goal is that a stimulus (usually visual) comes to acquire secondary reinforcing properties. To that end, animals have to

FIGURE 31.3 Overview of the drinkometer system to study alcohol drinking patterns in mice. This system is a fully automated, highly precise monitoring system for alcohol drinking in mice in the home cage that allows for detecting micro-drinking and circadian drinking patterns. The system is used to monitor simultaneously water and alcohol consumption as well as motor activity at high accuracy and in a high time resolution.

complete different trains of responding before obtaining the reinforcer. Thus, the completion of the requirements of a first operant schedule results in the presentation of an initially neutral stimulus. Satisfying the requirements of the second schedule (in the presence of the neutral stimulus) will result in the delivery of a reinforcer. Therefore, while the behavior for the final schedule would still be paired with a primary reinforcer, the behavior in the earlier component of the chain is maintained by the acquired motivational properties of a previously neutral event (Sanchis-Segura and Spanagel, 2006). A third most used schedule is the progressive ratio. Here, the required ratio increases following a predefined progression, and a "breaking point" is determined as the highest response rate accomplished to obtain a single reinforcer. This schedule is particularly useful in determining the relative reinforcement strength or reinforcing efficacy of the delivered reinforcer. Indeed, it has been reported that increasing the unit dose of the drug increases the breakpoint on a progressive ratio schedule (Roberts et al., 1989).

In summary, non-operant and operant drug self-administration procedures are considered to be valid and reliable models of human drug consumption. However, compared to the (technically) more simple non-operant procedures, the use of operant schedules provides more flexibility in the experimental design in addition to being more informative. In this context, it should be noted that operant procedures require learning abilities that can be a determinant factor in operant-based procedures and therefore a confounding factor.

A second group of methods used for assessing drug-induced reinforcement in laboratory animals includes the *conditioned preference* (CPP) tests. These tests, also called place conditioning, are non-operant procedures where the drug is administered by the experimenter and are based on classical or Pavlovian learning processes. In practice, the drug's effects, which functions as the unconditioned stimulus, are repeatedly paired spatially and temporally with an initially neutral stimulus (an environment). After repeated pairings, the drug-associated environment acquires the ability to act as a conditioned stimulus and will be able to elicit approach/avoidance behavioral responses depending on the nature of the used unconditioned stimuli (for a review see Tzschentke, 2007). According to this, it is suggested that these procedures can be useful in determining if a drug produces reward/aversion. In general, a higher number of pairings will strength the CPP, while in contrast, repeated exposures to the previously drug-associated environment without administering the drug will result in a reduction of the conditioning and subsequent extinction of the preference, a phenomenon also called Pavlovian latent inhibition. Thus, it is proposed that in addition to being useful in isolating the hedonic value or rewarding properties of a drug, this test also enables one to measure drug-seeking behavior. However, little is known about the psychological processes involved in the development and expression of such conditioned preferences. A similar procedure can be established in humans, as confirmed by recent human studies. Those studies have shown development of place preference using amphetamine (Childs and de Wit, 2009), food (Astur et al., 2014), or a secondary reinforcer (Astur et al., 2016). A modified version of place conditioning is the conditioning taste aversion tests (CTA). From an evolutionary point of view, the CTA is a Pavlovian learning process that develops after aversive post-ingestive consequences occur, so the taste will be avoided on later encounters (for a review, Lin et al., 2014). Thus, a solution (usually sucrose/saccharin) is paired with the unconditioned stimulus subject to study (ie, lithium chloride or other substances that induce aversion). Therefore, the CTA causes a reduction in the hedonic value of the taste-conditioned stimulus, a property commonly referred to as palatability, and such a reduction can be viewed as a consequence of the conditioned reduction in palatability. Intriguingly, when drugs of abuse are used as the unconditioned stimulus, instead of producing a positive emotional response, as observed in the CPP or self-administration paradigms, they result in the development of CTA. This topic has been a major focus of research in the last years (ie, why reinforcing drugs induce a CTA) with the two dominant explanations being that drugs of abuse have both rewarding and aversive properties and that drugs of abuse do not cause aversion but avoidance (which can be differentiated from aversion mainly as a non-emotional response) (Parker, 2003). However, this issue seems now to be solved, as recent results have indicated that drugs of abuse, in fact, induce CTA (Lin et al., 2014).

The last method presented here to evaluate the motivational properties of rewards is the *brain self-stimulation reward* paradigm. In 1953, James Olds and Peter Milner demonstrated in a series of experiments with rats that direct brain electrical stimulation (ie, intracranial self-stimulation, ICSS) was rewarding, leading to the conclusion that electrical brain stimulation (ie, brain stimulation reward) could serve as an operant reinforcer (Olds and Milner, 1954). Later on, the laboratory of Robert Heath demonstrated this phenomenon in humans, by modifying intracranial self-stimulation techniques for use with neuropsychiatric patients, which provided data suggestive of positive and negative reinforcing properties of brief electrical stimulation to various subcortical structures of the human brain (Bishop et al., 1963). In subsequent work, the study of the neuroanatomical and neurochemical substrates of ICSS suggested that ICSS activates neuronal circuits that are activated by natural reinforcers. Moreover, it is well accepted that ICSS might reflect the stimulation of the brain systems involved in motivated behavior, and thus the brain reward pathway (Carlezon and Chartoff, 2007). In the field of addiction, the intracranial self-stimulation paradigm

represents the principal technique to study behavioral consequences of alterations in the brain reinforcement system and reward processing. In brief, applied to rodents, it is an operant procedure in which responding is maintained by electrical brain stimulation within the mesolimbic dopamine system, including the medial forebrain bundle. Stimulation of this pathway produces reliable ICSS. This method is very reliable to quantify the acute reinforcement-potentiating effects of rewards by determining the minimum electrical stimulation required to sustain responding (the brain stimulation threshold, that is decreased by natural and drug rewards). The main advantage of this procedure includes its stability over the time, rendering it sensitive to changes produced by manipulations. Therefore, the ICSS represents a powerful and reliable behavioral measurement of the brain reward function over time.

In summary, animal studies of the motivational properties of rewards have allowed us to identify motivational and psychological processes involved in the initiation of drug addiction in humans (Table 31.3). In fact, these paradigms are more focused on the rewarding and reinforcing aspects of drugs, rather than in the generation of specific phenotypes relevant to addiction. Although these paradigms do not necessarily reflect an addictive behavior (described next), they are valuable in detecting the abuse potential of drugs.

Addictive Behaviors in Animals

Modeling the entire spectrum of a complex human mental disorder such as addiction in animals is not possible. Yet, based on the current psychiatric diagnostic classification system DSM-5, it is possible to translate anthropomorphic terminology into objective and behaviorally measurable parameters in animals. Thus, as will be described, currently, we are able to model at least some of the features that characterize the transition to addiction in humans. These addictive phenotypes include increased motivation for drugs, drug seeking, relapse, loss of control, and intake despite negative consequences.

A progressive *increase in the motivation for drugs* is one of the major hallmarks in the transition to addiction. In rodents the most commonly used tests capturing this aspect are the escalation of drug use and the progressive ratio schedule of reinforcement. The escalation effect refers to the progressive increase in the frequency and intensity of drug use, and it has good face validity. Thus, the drug is often taken in larger amounts and over a longer period that was intended (American Psychiatric Association, 1994). A key study with rats demonstrated that the pattern of drug exposure is critical in triggering this phenomenon. Thus, long-term exposure (or extended access) to cocaine (6 h) produced a particular pattern of drug use (compared to short-term exposures of 1 h), which was characterized by sustained higher intake over the time, suggesting an increase in hedonic set point (Ahmed and Koob, 1998). Similar results have been observed with other drugs (for a review, see Vanderschuren and Ahmed, 2013). Alcohol has also been widely studied in this aspect. An early study by Wise in 1976 already showed an escalation pattern on intake in rats exposed intermittently to alcohol (every second day) in the home cage. Later, Spanagel's lab extended these findings by showing that repeated periods of withdrawal from alcohol induced not only a progressive increase of alcohol intake over the time, but also a preference for higher ethanol concentrations (Spanagel and Hölter, 1999). Although the development of tolerance has been classically proposed to contribute to the escalating intake, other psychological, societal, and economic factors might also be involved (Ahmed, 2011). Last, it is worth mentioning here another animal model of excessive alcohol drinking following a history of dependence classically used to study the substrates of the "addicted brain" (for a review Spanagel, 2009). Thus, dependence is induced by exposing the animals during a period ranging from 4 to 8 weeks to intermittent ethanol vapor, and the increased ethanol self-administration observed after has been suggested to involve an allostatic-like adjustment in which the set point for ethanol reward is enhanced (Koob and Le Moal, 2001). The aforementioned escalation and excessive drinking patterns are associated with increased break points in the progressive ratio schedule of reinforcement (where the animals have to increase the number of responses for every subsequent reward), suggesting an increased motivation. Thus, the described studies performed with cocaine or ethanol that report an escalation intake after extended drug access have also reported increased break points (for review Vanderschuren and Ahmed, 2013; Spanagel, 2009). Additional evidence supporting parallel occurrence of drug escalation and increased motivation phenomenon comes from operant runaway procedures, where rats with extended access to cocaine were faster in reaching a goal box to receive a cocaine dose (Ben-Shahar et al., 2008). Overall, these studies show that extended access to the drug leads to excessive consumption and escalation of the drug intake over days, similar to the pattern of use seen in human addicts.

The most popular procedure to study *drug-seeking* behavior is the so-called reinstatement model of relapse to drug seeking. It refers to the resumption of drug seeking after extinction following exposure to drugs, drug cues or contexts, or stressors (Shaham et al., 2003). In this procedure, animals are first trained to self-administer a drug and then subjected to an extinction phase, where lever pressing or nose poking is extinguished in the absence of the drug. Once extinguished, animals are presented with several stimuli (without the drug reward) that will cause the renewal of the responding (reinstatement of drug-seeking

behavior). Thus, the ability of the exposure to the stimuli to reinstate drug seeking is determined under extinction conditions. Importantly, this method appears to resemble the factors that trigger craving and relapse in humans, and it reflects the increased development of preoccupation to access the drugs. That is, similar to the human situation, three events can reinstate the drug-seeking behavior in this model: drug priming (or a small drug dose), stress, and conditioned/contextual stimuli. This model has some degree of pharmacological validation: the anti-craving and anti-relapse drugs acamprosate and naltrexone, known to be effective in alcoholic patients, are able to reduce cue-induced reinstatement of alcohol-seeking behavior in rats (Katner et al., 1999; Batchteler et al., 2005). An alternative approach consists of assessing priming-induced drug seeking by the use of CPP paradigm.

Besides, by particularly examining the responding rates during extinction, this procedure allows for studying the difficulty abstaining from drugs that characterize addicted humans (ie, resistance to extinction). Results from several studies indicate that increased self-administration experience and the length of the withdrawal period are critical factors influencing the resistance to extinction (Vanderschuren and Ahmed, 2013). Actually, the latter has been extensively studied by Shaham's lab in the so-called incubation of drug craving model. This model is based on the early observation in humans made by Gawin and Kleber (Gawin and Kleber, 1986), who proposed that cue-induced cocaine craving progressively increases over the first weeks of abstinence and remains high over extended periods. Thus, this phenomenon was subsequently identified in rats and for other natural or drug rewards like methamphetamine (Shepard et al., 2004), alcohol (Bienkowski et al., 2004), nicotine (Abdolahi et al., 2010), and sucrose (Grimm et al., 2002) and consists in time-dependent increases in extinction responding and cue-induced reinstatement after cessation of drug self-administration training (Grimm et al., 2001; Neisewander et al., 2000; Shalev et al., 2001).

A third addictive trait is *relapse after a period of deprivation*. It can be defined as the recurrence of a past condition, namely excessive and uncontrolled drug taking after a phase of abstinence (Vengeliene et al., 2014). The most studied model is the alcohol deprivation model, which provides excellent face validity to relapse behavior seen in alcoholics. A series of experiments performed in rats, mice, and monkeys 30−50 years ago described that, in animals given voluntary access to alcohol for a certain period of time and then deprived for several days/weeks/months, representation of alcohol lead to a robust but temporary increase in alcohol intake over baseline drinking, referred to as the alcohol deprivation effect (ADE) (Sinclair and Senter, 1967; Salimov and Salimova, 1993; Sinclair, 1971). The genetic make-up of the animal, concurrent access to more than one alcohol concentration, the duration of access to alcohol, and the length of abstinence are all factors influencing the magnitude of the ADE (for review, Vengeliene et al., 2008, 2014). It is important to mention that this model has been validated pharmacologically using acamprosate (Spanagel et al., 2014b), naltrexone (Hölter and Spanagel, 1999), and nalmefene, which are abstinence-promoting drugs used in the treatment of alcohol-dependent patients, thus demonstrating an excellent predictive validity for the human condition. Hence, this model represents the standard in examining the efficacy of putative pharmacological agents for preventing alcohol relapse (ie, Spanagel and Vengeliene, 2013). Other models of relapse to cocaine or alcohol have developed operant self-administration procedures. These models resemble more the voluntary abstinence and the compulsive relapse typically observed in humans. To this end, rats have to abstain responding to the drug when an aversive stimulus is presented (self-imposed abstinence) and resume the instrumental responding when the aversive stimulus is removed (relapse) (ie, Economidou et al., 2009; Marchant et al., 2014). By the use of this procedure, the psychobiological mechanisms of both abstinence and relapse can be explored.

Another core feature of addictive behavior is the *loss of control and compulsivity*. In fact, solid evidence supports a link between impulse control disorders and drug addictions (Grant, 2008). Indeed, addictive behavior in most cases is characterized as compulsive, and there is a progressive loss in the ability to refrain from drug-related behaviors (Spanagel and Heilig, 2005). In laboratory animals, this loss of control can be assessed by measuring the impulsive choice trait, defined as high preference for small and immediate rewards over larger and delayed rewards. The procedure used to measure this aspect is the temporal discount paradigm, where the animal is presented with those two behavioral alternatives, and the choice of a small and immediate reward is considered impulsive. This procedure resembles the higher rate of discount displayed by drug addicts in similar tasks and therefore has face and constructs validity (Kirby and Petry, 2004). In addition, loss of control over behavior might also result from neurocognitive deficits, well documented in drug addicts (reviewed in Franken and van de Wetering, 2015) and might include among others, attention, memory, or decision-making processes. In the past years, a growing body of animal studies has addressed this particular relationship (Vanderschuren and Ahmed, 2013). Thus, several studies have reported deficits in diverse cognitive functions, including attention, working memory, cognitive flexibility, object recognition memory, and impulsive behavior in rats or primates self-administrating cocaine, methamphetamine, MDMA (3,4-methylenedioxymethamphetamine), or heroin (ie, Briand et al., 2008; Dalley et al., 2005a,b; 2007, 2008; Parsegian et al., 2011; Porter et al., 2011; Schenk et al., 2011; Schippers et al., 2012). However, it still remains to be elucidated

whether those neurocognitive and impulse control disorders are in some cases present before the drug experience, therefore predisposing the addictive behavior in vulnerable individuals (see next section).

The last key feature of addictive behavior presented here is *drug intake despite the knowledge of negative, adverse consequences*. Certainly, this aspect is directly related to the previously described loss of control over behavior, in the sense of a reduced behavioral elasticity. That is to say, the compulsive behavior already described involves an irresistible urge to take the drug regardless of whether it will result in adverse consequences. Therefore, animal paradigms capturing this behavior should reproduce a persistent (ie, lack of elasticity) drug seeking or intake in spite of adverse or negative consequences (ie, punishment). Irrespective of the paradigm used, animal studies have consistently indicated that after prolonged exposure to drugs, similar to humans, drug seeking and intake becomes progressively insensitive to punishment signals. For example, in conflict paradigms, where there is a simultaneous delivery or pairing of the drug and an aversive stimulus (like foot shock or lithium chloride injection), rats with a long history of cocaine or alcohol intake did not considerably reduce the consumption (Corbit et al., 2012; Cunningham, 2000; Deroche-Gamonet et al., 2004; Dickinson et al., 2002). Importantly, this resistance to punishment has a psychological nature, and is not related to pharmacological interactions (like analgesic or anxiolytic properties of some drugs); this was demonstrated by Vanderschruen and Everitt (2004) by showing that an aversive-conditioned stimulus (like a tone paired to a foot shock) had a similar effect as the unconditioned stimulus (foot shock) in long-term cocaine self-administering rats. In the context of alcohol, the previously described ADE can also be used as a model equivalent to human drug intake despite adverse consequences. Thus, with repeated deprivation phases, a compulsive drinking pattern arises during a relapse situation, characterized by insensitivity to taste adulteration with quinine, loss of circadian drinking patterns during an ADE, and a shift toward consuming highly concentrated alcohol solutions to rapidly build up blood alcohol concentrations and produce intoxication (Vengelinene et al., 2014). The lack of sensitivity to quinine adulteration has also been demonstrated in chronic intake of opiates, amphetamine, and nicotine (Galli and Wolffgramm, 2011; Heyne, 1996; Heyne and Wolffgramm, 1998; Wolffgramm and Heyne, 1995). Together, all these studies concluded that a long-term experience of drug taking is enough to sift the behavior in some individuals from controlled, goal-directed behavior to a compulsive, insensitive to punishment behavior.

As described earlier, due to the complexity of the addiction phenomenon, preclinical and basic research has focused on those addictive behaviors that model different characteristics of the addictive syndrome in humans. However, it is noteworthy to mention here an exceptional animal model developed that best captures addictive behavior as a whole in rats. This model, established by Piazza's group is called the three-criteria addiction model for cocaine (Deroche-Gamonet et al., 2004) and consists of various measurements (three criteria) that reflect the motivation for the drug. These criteria resemble three of the essential diagnostic criteria for addiction and include high motivation to obtain the drug, persistence of drug seeking in the absence of drug (or resistance to extinction), and motivation to obtain the drug despite negative consequences (resistance to punishment). In the original article, the authors demonstrated that these three addiction criteria appear over time in rats trained to self-administer cocaine, and they provide an "addiction score" that correlates with the degree to which re-exposure to cocaine reinstates responding to the drug (Deroche-Gamonet et al., 2004; Belin et al., 2009). Furthermore, an early burst-like patterns of cocaine use is predictive of later high "addiction scores." The final score is the summary of the outcome of three measures, those measures being independent, and each rat may exhibit only one, two, or all three aspects of addiction. More importantly, the results obtained with rats resemble the human situation, as this addiction-like behavior is present only in a small proportion of humans using cocaine and is highly predictive of relapse after withdrawal. Thus, closely similar to the humans, 41.4% of the rats did not show any criteria, while 27.6% were positive for the presence of one criterion, 13.8 for two criteria, and 17.2% were positive for three criteria. Another important aspect of this three-criteria model is that it integrates both experimental and clinical perspectives, and thus shows that the development of addiction depends on the interaction between long drug exposure and individual vulnerability.

In summary, we have shown how both reward-induced motivational processes and some of the key symptoms of addictive behavior can be reproduced in animals (high motivation, drug seeking, relapse, loss of control, and drug intake despite negative consequences), and therefore they can be used to study the psychobiological mechanisms underlying addiction in humans (Table 31.4). Importantly, these studies have also led to the common conclusion that the development of addictive behaviors depends not only on certain environmental circumstances (like prolonged drug access) but also on individual differences that predispose the addictive behavior. Next, we will describe some vulnerability factors leading to addiction.

THE DIVERSITY IN TRANSITION TO ADDICTION: VULNERABILITY FACTORS

The transition to addiction is heavily influenced by biological, personality, environmental and genetic factors and their dynamic interactions, which will determine the course

TABLE 31.4 Main Addictive Phenotypes and Tests Used in Animals to Model Addiction Traits in Humans

Human trait	Animal phenotype	Test
Increased motivation	Escalation Increased intake	Extended access Alcohol vapor exposure Progressive ratio Operant runaway Three-criteria model
Craving and relapse	Drug seeking after extinction Increased drug taking after withdrawal	Cue, context, priming, and stress-induced reinstatement after extinction Incubation effect ADE Three-criteria model
Loss of control	Preference for small and immediate rewards Neurocognitive deficits	Delay discounting Decision-making Three-criteria model
Intake despite negative consequences	Insensitive to punishment signals	Conflict paradigms Taste adulteration during ADE Three-criteria model

and severity of the addiction. Although those factors can also be protective, here I will give an overview of the susceptibility factors that increase the risk of developing addictive-like behaviors.

Biological and Developmental Factors: Gender and Adolescence

Gender

As the reader might have already noticed from his/her own experience (most probably with alcohol), men and women react differently to drugs. Certainly, gender differences are present across the whole addiction cycle, which includes initiation, maintenance, and progression to addiction, with withdrawal followed by relapse. In general, the gender-related differences are maintained regardless of the drug, though specific drug × sex-dependent different patterns also exist (which will not be discussed in detail here).

Epidemiological studies have observed significant gender-specific differences in patients with addiction disorders (Hudson and Stamp, 2011). For instance, the prevalence of drug abuse like alcohol, psychostimulants, and narcotics is higher in males than in females (Tetrault et al., 2008; Brady and Randall, 1999). Intriguingly, addiction-related behaviors seem to be stronger in females. Thus, women begin using drugs younger, escalate drug use faster and experience shorter periods of drug abstinence (Brady and Randall, 1999). Consequently, women show higher propensities to relapses (Kosten et al., 1993; Becker and Hu, 2008) with longer periods of drug use before abstaining (Gallop et al., 2007; Anker and Carroll, 2010). In an attempt to explain these apparent contradictory findings, it has been proposed that the difference in the rate of drug use may not be directly related to gender vulnerability, but other societal factors (Van Etten and Anthony, 2001). However, it must be kept in mind that the prevalence of some psychiatric disorders is higher in women, some of which are vulnerability factors for addiction (like anxiety, stress, or depression; see other section) (reviewed in detail in Bisagno and Cadet, 2014). In general, these different patterns between males and females, being more males with addiction disorders, and females suffering more severe addiction problems, have been shown by clinical studies with stimulants, opiates, nicotine, and alcohol (reviewed in Becker and Hu, 2008). Importantly, it is suggested that the enhanced subjective ratings experienced by drugs in females might contribute to the higher vulnerability to addiction, a phenomenon called "telescoping"; this phenomenon has been already reported for cannabis, alcohol, and cocaine (Cooper and Haney, 2014; Piazza et al., 1989; Becker and Hu, 2008). Despite this evidence, it must be noticed that the pronounced differences between men and women have been declining, and the misuse of drugs and alcohol in women is rapidly approaching that of men (Becker and Koob, 2016). Stress and emotional factors have been proposed as potential mechanisms underlying these gender differences in addictive behaviors. In particular, the higher relapse risk in females has been associated with negative emotional states induced by stress and depression (Zilberman et al., 2003; Carroll et al., 2004). Supporting this, a study (Potenza et al., 2012) has reported that the brain activation induced during craving is triggered by stress cues in females and drug cues in males. In addition, hormonal changes might also affect the response to drugs. Thus, females report higher positive effects from drug taking during their menstrual cycle (Evans et al., 2002), and estrogen administration has a positive effect on

dopamine activity (Di Paolo et al., 1988; Levesque et al., 1989). On the other hand, progesterone administration has the opposite effect, reducing dopamine and subjective positive responses to drugs in males (Fernandez-Ruiz et al., 1990; Sofuoglu et al., 2004).

Similar to humans, extensive preclinical research with laboratory animals has found gender differences across different addictive phenotypes and mechanisms; in fact, what can be generally concluded from animal studies is that gender differences related to addiction do occur in rodents and can be paralleled to those of humans (a detailed review is provided by Becker and Koob, 2016). In general, and as reported in humans, animal studies using rodents have reported the presence of gender differences across the whole addiction cycle. Thus, female rats acquire self-administration of drugs and alcohol faster than males, indicating a faster initiation of drug use. After chronic use, the intake of drugs during escalation and with extended access is as well faster compared to males. Regarding the withdrawal and craving stage, females show more motivational withdrawal and greater reinstatement of drug-seeking behavior. Interestingly, female rats show less motivational withdrawal from alcohol. These findings have led to the suggestion that alcohol might have exclusive gender-related differences (Becker and Koob, 2016). The influence of hormonal/emotional and stress factors have also been proposed as potential mechanisms. For example, gonadal hormones seem to be important, as adult ovariectomized females resemble the male phenotype and the menstrual cycle/estrous cycle in females induces some, although minor, behavioral alterations. In some cases, changes in drug seeking have been observed after progesterone and estradiol treatments, with the former attenuating and the later potentiating the behavior. These hormonal effects, however, do not appear to affect advanced stages of addiction, as compulsive drug taking is not affected by these hormonal alterations. Another vast line of research comes from the differential neural changes associated to addiction in males and females. These studies have focused mainly in alterations in neurotransmission induced by drugs of abuse during the different stages of the addiction cycle. Overall, these studies have reported quantitative and qualitative differences between males and females in key neurotransmitter systems associated with the stress and negative affective states occurring during the withdrawal stage. In particular, these differences were found in the corticotrophin releasing factor and the opioid dynorphin neurotransmitters, both of which are critically involved in hormonal and behavioral responses to stressors.

In summary, gender represents a key factor of vulnerability to develop addiction, and differences in responses to drugs of abuse have been reported both in human and in laboratory animals. Clinical and preclinical research has revealed that females are more vulnerable from the initiation of drug use to the withdrawal and relapse stages. These differences have been attributed to hormonal and stress/emotional factors, suggesting an important role of ovarian hormones and stress in influencing vulnerability to drug abuse and addiction.

Adolescence

Three aspects render adolescence a critical vulnerability window for developing addiction: first, an immature, developing brain; second, a risk-taking behavior, including drug experimentation; and third, the (social) environment. Consequently, initiation of abused drugs use during adolescence might lead to impaired psychological, cognitive, and affective development, and later addiction. Indeed, the striking increase in prevalence rates from ages 13 to 18 highlight adolescence as the key period of development of substance use disorders (Merikangas and McClair, 2012).

Some of the characteristics of the developing brain during adolescence might underlie the vulnerability to addiction. Psychological and imaging studies show that the underlying immature neural substrates of self-control (reviewed by Paus, 2005), decision-making, impulse control, and cognitive processes constitute risk for substance used disorders, while reward-related processes show the classic inverted U-shape that typifies the peak of high-risk behavior during adolescence (Casey and Jones, 2010). In particular, changes in the dopamine system during adolescence have been extensively studied (reviewed in detail in Ernst and Luciana, 2015). First, alterations in the dopaminergic reward system have been reported, with high densities of the dopaminergic D1 and D2 receptors in the adolescent striatum (Goto et al., 2007). This upregulated circuit might ultimately facilitate aspects of drug reinforcement and learning that are mediated, as mentioned earlier, by dopamine signaling. The peak expression of this specific receptor population during this stage is likely to motivate adolescents to seek hedonic-related substances more than any other age group and also plays a role in novelty preferences and impulsive choice (Sonntag et al., 2014). In fact, the mere experience or anticipation of rewards (that may include substances of abuse) causes a stronger activation in reward-relevant structures within the dopaminergic system of adolescents relative to children and adults (Ernst and Luciana, 2015). In addition, this striatal dopamine signaling might interact with the delayed and protracted maturation of cortical control systems within the prefrontal cortex relative to incentive- and stress-based subcortical systems (Selemon, 2014; Somerville et al., 2010). Moreover, it has been proposed that such alterations might contribute to addictive phenotypes, in the form of hyperresponsiveness to rewards (Braams et al., 2015) and lack of self-restraint and emotional regulation ability (Casey and Jones, 2010). Besides, these two aspects (high

reactivity to rewards and lack of emotional regulation) might also potentiate approach behavior, enabling contact with reward-related contexts, despite of the risk that might include. This idea is supported by the following findings: first, the social, sexual, and other risk-taking behaviors (Eaton et al., 2012) characteristic of adolescents; second, self-reports of reward reactivity and sensation seeking (ie, Harden and Tucker-Drob, 2011); and third, neuroimaging studies showing brain responses in reward processing (ie, Richards et al., 2013).

Preclinical studies have confirmed and extended the aforementioned findings. More specifically, it has been reported that the developmental increase in dopaminergic and glutamatergic interactions influence sensitivity to cue-induced seeking, extinction, and reinstatement (ie, Kalivas, 2005; Badanich et al., 2006; Ventura et al., 2007; Andersen et al., 2008; Brenhouse et al., 2008), as well as the rewarding nature of cocaine and nicotine (Thiel et al., 2008, 2009) by elevating motivational salience in adolescent rats. Another study found that risk-taking behavior in adolescent rats was a predictor of cocaine self-administration in adulthood and was linked to striatal function (Mitchell et al., 2014).

Environmental factors also play a critical role in the adolescence susceptibility to addiction. Thus, during adolescence, individuals learn to engage in dynamic and flexible relationships in the context of social development. Animal studies have reported the effect of social experience on both neuronal and behavioral developments. These studies have demonstrated that social isolation during the peri-adolescence period of rats results in a heightened locomotor reactivity to novelty and behavioral sensitivity to psychostimulant drugs (Baarendse et al., 2014; Fone and Porkess, 2008) as well as increased alcohol consumption (Lesscher et al., 2015). Further, another set of studies demonstrated that social isolation affects prefrontal and striatal circuits (Bianchi et al., 2006; Dalley et al., 2002; Hall et al., 1998). In line with this, an environmental enrichment has opposite effects on drug taking. Access to exercise (wheel running) in the home cage is a classically used animal model of environmental enrichment. Recent studies have demonstrated that chronic exercise reduces rewarding properties of cocaine, cocaine intake during extended access, and cue-induced nicotine seeking behaviors in adolescents compared to adult rats (Thanos et al., 2010; Zlebnik et al., 2012; Sanchez et al., 2013).

Taken together, this brief overview indicates that adolescence is a crucial time for the development of drug use and addiction. Besides other factors (not discussed here, like familiar, societal, or internal factors), an immature brain, more sensitivity to drugs, and psychological traits that favor reward-related behaviors may represent key factors that contribute to it.

Personality Traits and Psychiatric Disorders

Anxiety

From epidemiological studies, the idea of a predisposition to addiction in individuals with preexisting psychological and emotional disorders including anxiety has been already reported (Rounsaville et al., 1991; Merikangas et al., 1998; Marquenie et al., 2007). In humans, preexisting high anxiety (or trait) appears to have an impact on cocaine treatment outcome and to be positively correlated with negative consequences due to cocaine use. Moreover, this same study showed a positive correlation of anxiety with the Alcohol Composite Index of the Addiction Severity Index (ASI) (O'Leary et al., 2000). In fact, anxiety might be a particularly important predisposing factor for alcohol addiction in individuals more sensitive to its anxiolytic actions. The notion that anxiety might trigger alcohol consumption is based on the "tension reduction hypothesis" of Conger (1956), which proposed that alcohol consumption may be found to be anxiety reducing, which then reinforces alcohol consumption and promotes future alcohol intake: the ingestion of alcohol may be an attempt to self-medicate against anxiety symptoms (Spanagel, 2009). Interestingly, clinical studies have reported that anxiety disorders predict a faster progression from age at first drink and regular drinking to the onset of alcohol dependence (Sartor et al., 2007; Kushner et al., 2012).

At a preclinical level, anxiety measurements consist of assessing the natural fear of rats and mice to open, high, and brightly lit spaces. The most commonly used apparatuses are the elevated plus maze (EPM, consisting of two open and two closed arms in a "plus" shape and elevated from the floor) and the light–dark box (a box divided in two compartments, one of them is highly illuminated). Exposure of the animals for a short period of time (ie, 5 m) provides a fast and simple measurement of the basal anxiety level. In animal studies, the relationship between preexisting anxiety and predisposition to addictive-related behaviors has been preferentially studied in the context of cocaine and alcohol-related responses. Pelloux and colleagues found that in rats classified as anxious or non-anxious on the basis of their performance on both the EPM and light–dark box tests, the anxious animals experienced higher rewarding effects of cocaine, as measured in the place conditioning paradigm (Pelloux et al., 2009). High basal anxiety levels also predicted increased oral cocaine consumption compared to non-anxious animals (Walker et al., 2009). Rats that spent more time self-grooming (a behavior indicative of high anxiety in rodents) during the exposure to the EPM show a higher breakpoint tested in the progressive ratio schedule of reinforcement, indicating a higher motivation for cocaine (Homberg et al., 2002). More recently, it was shown that

rats showing high anxiety levels in the EPM showed a higher loss of control over cocaine (but not heroin) intake, as indicated by escalation of cocaine self-administration (Dilleen et al., 2012). Regarding alcohol, it has been shown that elevated levels of anxiety as assessed in the EPM correlate not only with high voluntary alcohol consumption during the initiation of alcohol drinking behavior but also with high preference for alcohol (Spanagel et al., 1995; Henniger et al., 2002) and, more importantly, during limited or continuous access to alcohol (Hayton et al., 2012). In mice, high anxiety levels are also predictors of greater consumption and preference for ethanol than low-anxious mice (Bahi, 2013). In fact, genetically selected alcohol-preferring lines are more anxious than their non-preferring counterparts, like the Sardinian (Colombo et al., 2006) and the Marchigian Sardinian (Ciccocioppo et al., 2006) Italian rat lines. Furthermore, only rats selected as anxious show increased rewarding effects of alcohol in the CPP paradigm (Blatt and Takahashi, 1999). A study analyzed the relationships between ethanol consumption in situations favoring excessive or limited intake or after deprivation and preexisting levels of anxiety and found that anxiety was associated with a quicker recovery of ethanol consumption after the concentration drop and a greater increase in ethanol consumption after deprivation (Pelloux et al., 2015).

Novelty Seeking

Considerable evidence supports the idea that novelty or sensation seeking in adult humans (adolescence will not be introduced here) is highly predictive of addictive disorders. Early studies have already shown that novelty or sensation seeking is a common personality trait encountered in drug addicts, which could preexist (Cloninger et al., 1993). In line, high novelty seekers do prefer stimulant drugs (Khantzian, 1985) and consumed earlier and more varied drugs in comparison with the general population (Sutker et al., 1978; Cloninger, 1987). In addition, high novelty seeking or sensation seeking has been associated not only with an increased frequency and amount of drug use, but also with an increased risk for developing addiction (Hawkins et al., 1992). A study performed with almost 9000 adults has found associations with the use of alcohol, cannabis, and cocaine (Schneider et al., 2015). The main hypothesis supported by most of the clinical studies proposes that an individual displaying high novelty seeking can be vulnerable to addiction due to increased sensitivity to the reinforcing effects of drugs. Thus, in an interesting study by Leyton et al., a positive correlation was found between novelty seeking, amphetamine-induced drug wanting, and amphetamine-induced dopamine release (Leyton et al., 2002). In line with these results, Kelly et al. found that individuals with high sensation seeking showed greater sensitivity to the psychostimulant-like effects of amphetamine on self-report measures that were associated with the reinforcing effects of drugs (Kelly et al., 2006).

Evidence from animal studies has also supported the clinical findings. Thus, using different versions of procedures based on the measurement in an activity chamber of the preference for novelty versus a familiar environment, rodents can be classified into high and low novelty seekers. Pioneer studies by Piazza showed that rats showing a higher locomotor response in a novel environment have a higher propensity to acquire psychostimulant self-administration, and they self-administer more cocaine than the low responder rats (ie, lower locomotor activity) (Piazza et al., 1989, 2000). These results were confirmed and extended by Belin, who showed, using another procedure, that high novelty seeking rats showed a stronger vulnerability to develop compulsive cocaine self-administration (Belin et al., 2008, 2011). Additional studies have shown a positive correlation of novelty preference with oral consumption of amphetamine and morphine (Pelloux et al., 2004, 2006), and greater CPP induced by morphine (Zheng et al., 2003; Pelloux et al., 2006), amphetamine (Robinet et al., 1998; Klebaur and Bardo, 1999) or cocaine (Vidal-Infer et al., 2012). Last, a study has shown that spontaneously hypertensive rats show high levels of novelty seeking and enhanced sensitivity to the reinforcing effect of methylphenidate (dela Pena et al., 2015).

In the field of alcohol, the association of novelty and alcohol-related responses has been more controversial, with some studies reporting no positive correlation (ie, Bienkowski et al., 2001; Nadal et al., 2002; Hayton et al., 2012; Manzo et al., 2014), while others did (Manzo et al., 2014). However, a 2015 study might solve these discrepancies. Here, assessment of the relationship between novelty-induced place preference and ethanol intake in rats supports a positive correlation. Thus, in this study, it is shown that in situations favoring excessive or limited intake or after deprivation, high novelty seeking rats consume more alcohol than the low novelty seekers. In view of these results, it has been suggested that high novelty/sensation seeking individuals may be consuming drugs in higher levels as a means to experience a new, intense, and complex subjective state (Pelloux et al., 2015).

Impulsivity

In the last decades, impulsivity or impulse control disorders have been considered as an important personality trait or psychiatric condition in the development of addictive disorders. In fact, impulse control, also considered as a behavioral addiction, shares common features with addiction disorders, including a craving state preceding compulsive behavior, impaired control over behavior, and

behavioral persistence despite adverse consequences (Grant, 2008). Furthermore, similarities between these two disorders can also be found at a neurobiological and neurocircuitry levels. The most widely studied behavioral facets of impulsivity both in humans and animals include the action/motor and choice impulsivity using different tasks or tests (detailed in Mitchell and Potenza, 2014).

Although in the addiction research field impulsivity has classically been studied in the context of a comorbid disease (where the disease might or might not come as a consequence of drug use), in the last years some clinical evidence is emerging supporting impulsivity as a preexisting factor in addiction disorders. In a series of interesting studies performed with psychostimulant-addicted and healthy siblings, Ersche and colleagues showed similar impairments in impulsivity tasks and structural alterations, with the addicted group showing more pronounced alterations (Ersche et al., 2012a). Moreover, the cognitive and emotional profiles of the healthy, non-addictive siblings were characterized by deficits in executive function, such as working memory and mental planning, and high levels of anxiety and stress sensitivity (Ersche et al., 2012b). The notion that predisposing differences in impulsivity may contribute to potentiate or develop addictive behaviors has become an area of extensive preclinical research with different animal models of impulsivity. Thus, high impulsivity in rats and mice predicts the vulnerability to alcohol consumption (Poulos et al., 1995; Perry et al., 2005; Radwanska and Kaczmarek, 2012) and methylphenidate (Marusich and Bardo, 2009), but it does not predict heroin self-administration (McNamara et al., 2010; Schippers et al., 2012). Impulsive choice on a delay-discounting task predicts a more rapid acquisition and escalation of cocaine self-administration (Anker et al., 2009; Perry et al., 2005). Impulsivity (choice) may also predict resistance to extinction and increased relapse to both nicotine and cocaine (Diergaarde et al., 2008). An interesting study found that exposing animals to delayed rewards resulted in an increased alcohol self-administration as compared to animals exposed to prolonged rewards (Stein et al., 2013). Dalley and colleagues have extensively studied a specific form of impulsivity with the use of the five-choice serial reaction time task, which captures waiting impulsivity that can be paralleled to the human continuous performance test of sustained attention. They have shown that excessive and persistent failures to inhibit anticipatory responding (and thus high impulsivity) on this task predicted escalation of cocaine and nicotine self-administration (Dalley et al., 2007; Diergaarde et al., 2008), increased intake and sensitivity to sucrose (Diergaarde et al., 2009), increased the propensity for relapse following voluntary abstinence (Economidou et al., 2009), and elevated cocaine self-administration despite negative consequences (ie, punishment) (Belin et al., 2008).

Environmental and Social Factors

Epidemiological studies have shown the complexity of the environmental and social factors affecting drug addictive behaviors in a negative way. Among others, environmental factors include drug addiction of one or more family members, family conflict, lack of child supervision by parents, parental unemployment (especially fathers), and parents with low literacy. Some of the social factors include school, friends, unhealthy entertainment, unemployment, lack of social acceptance, cultural poverty, population growth, and uncontrolled migration. Given this scenario, it is obvious that disentangling the specific contribution of each variable to addiction-related problem is not a realistic option. However, a meta-analysis (Aghaii et al., 2012) integrating the results of different studies to investigate the impact of environmental versus social factors in people's tendency to become addicted found a greater relationship between environmental factors than other social factors, indicating that at least between those two, environment seems to be more important than societal variables in promoting drug use and abuse. However, emerging evidence supports an important role for societal factors.

Environment

In an attempt to better understand the contribution of the aforementioned environmental variables, the field of clinical and preclinical addiction research has proposed that the environment can affect addictive behaviors in three ways: adverse life experiences (ie, stress), enhanced drug-associated learning, and the environment associated to drug taking. At a clinical level, in general, due to the intrinsic difficulties and limitations of controlling many of the mentioned variables, human studies have not always provided enough evidence for a relationship between environment and addiction in humans. This is particularly the case when assessing stress impact on addiction. Thus, human studies have mostly focused the attention on the individual history of adverse life experiences and drug addiction. For instance, events as different as sexual abuse/harassment, combat-stress, occupational stress, marriage dissatisfaction, and physical traumas have been linked to the abuse of psychostimulants, opioids, and alcohol, and adverse childhood experiences play an important role in the susceptibility to drug abuse (for detailed references, Caprioli et al., 2007). In this context, stress effects on alcohol have been a main focus of research. In general, various laboratory stressors have been examined for their effects on alcohol self-administration, and the results vary depending on the experimental stressor chosen and many other factors (reviewed in Spanagel et al., 2014a). The effects of drug-conditioned associations (that is, Pavlovian conditioning: initially neutral environmental stimuli paired with the drug experience) have been almost exclusively

studied in the context of prevention, aiming to identify the neurobiological basis of craving and relapse. In the 1980s, drug-conditioned associations were described in humans to induce withdrawal-like symptoms and craving (Childress et al., 1984, 1986). In this context, the work from Volkow using imaging techniques has provided a great advance showing neurobiological changes associated to cue-induced craving (for a review see Volkow and Morales, 2015). Besides stress and drug-related learning, early studies pointed out that the setting where the drug is consumed importantly influences the drug experience in terms of behavioral and psychological responses (ie, Kelleher and Morse, 1968). Again, in this particular context, human evidences are not too much. A clear example is represented by MDMA, which is exclusively consumed in clubs (Parrott, 2004; Schifano, 2000). Two other studies were performed in the context of alcohol and amphetamine (Sher, 1985; Zacny et al., 1992). However, emerging evidence suggests that the degree of promoting drug use of some environmental settings is particularly associated with specific drugs, at least cocaine and heroin. Retrospective studies have shown that while heroin is used preferentially at home, cocaine is preferentially consumed outside the home (Caprioli et al., 2009; Badiani and Spagnolo, 2013).

In sharp contrast to the human research, preclinical models have extensively addressed the effect of environmental factors using animal models of addictive behaviors. One of the most studied variables to assess adverse life experiences in adult animals is stress. Thus, a variety of physical stressors (like electrical foot shock, tail pinch, or immobilization) have been reported to increase self-administration of many drugs, including cocaine, morphine, alcohol, and amphetamine (Goeders and Guerin, 1994; Goeders, 2002; Mantsch and Katz, 2007; Shaham and Stewart, 1994; Anisman and Waller, 1974; Volpicelli et al., 1990; Piazza et al., 1990; Shaham, 1993). More importantly (from a therapeutic approach, at least) is the effect of stress-induced reinstatement of drug seeking. Developed by Shaham in 1993, the stress-induced reinstatement (induced by physical or pharmacological stressors) represents today a solid and unequivocal paradigm to be used in laboratory animals, and it has been shown to trigger drug seeking of virtually all drugs of abuse (Bossert et al., 2013). Similar to human research, the effect of stress on alcohol seems to be particular. Thus, the general conclusion from most of the studies indicate that chronic stress, especially when administered early in development, results in elevated drinking later in adulthood. Moreover, the studies have demonstrated that alcohol represents itself a potent stressor, especially when consumed chronically, which then leads to escalation of voluntary alcohol consumption (for a review, see Becker et al., 2011). However, it seems that stress effect on alcohol intake might strongly depend on the experimental setting (ie, home cage drinking versus operant self-administration, Spanagel et al., 2014a). Regardless of the drug, there is vast evidence suggesting that an increased activation of the corticotropin-releasing factor (particularly within the extended amygdale) may mediate stress-induced reinstatement, and several additional stress-related neuropeptides have also been proposed (for a review on this topic see Spanagel et al., 2014a; Schank et al., 2012). The cue-induced reinstatement has a particularly relevant preclinical interest in the context of Pavlovian conditioning processes and the ability to trigger drug seeking even after long periods of abstinence. Thus, similar to stress, a vast literature has reported that drug-paired cues (contextual, discrete, or discriminative) can reinstate drug seeking after extinction of operant responding (Bossert et al., 2013). As we pointed out before, a third environmental variable that can alter the behavioral, subjective, and rewarding effects of a given drug is the drug-surrounding setting. Emerging evidence suggests that the degree of promoting drug use of some environmental settings is particularly associated with specific drugs, at least cocaine and heroin. Retrospective studies have shown that while heroin is used preferentially at home, cocaine is preferentially consumed outside the home (Caprioli et al., 2009; Badiani and Spagnolo, 2013). These human results were elegantly confirmed in a set of studies carried out by Badiani and colleagues showing how the setting influences drug taking and drug preference (Caprioli et al., 2009, 2007; Celentano et al., 2009; Montanari et al., 2015). In these experiments, rats were self-administering cocaine and heroin intravenously either in their home cage (the resident group, meaning that they were kept in the self-administration chamber during the whole experiment) or in a distinct environment (the non-resident group, where they were kept in the self-administration chamber only during the self-administration sessions, being then returned to their home cage). Interestingly, the results showed that, similar to humans, cocaine self-administration was greater and more rewarding in non-resident rats than in resident rats, whereas the opposite was true for heroin. Furthermore, when rats were given the opportunity to choose between heroin and cocaine, they exhibited distinct preferences as a function of context. Thus, of rats trained to self-administer for both cocaine and heroin within a session, most non-resident rats preferred cocaine to heroin, whereas resident rats tended to prefer heroin. Importantly, these heroin- and cocaine-associated specific environments also differ in their ability to reinstate drug seeking after a period of abstinence, with heroin priming being much more effective in resident than in non-resident rats, while cocaine priming was much more effective in non-resident than in the resident rats.

Social

The impact of the individual social environment on addictive behaviors has become a main focus of research in the last years. In fact, the social environment serves as the context in which drug use occurs. Only to mention a few human examples, social isolation and social ridicule are associated with higher rates of drug use (Aloise-Young and Kaeppner, 2005; Pearson et al., 2006; Rusby et al., 2005). Particularly, social stressors have also a consistent effect in promoting alcohol craving and consumption (reviewed in Spanagel et al., 2014a). In this context, it is believed that there are two aspects that are important for understanding their impact on vulnerability to drug abuse: (1) the emotional valence of the social experience and (2) the context in which the social interaction occurs, within or outside of the drug-taking context.

A body of animal studies has focused on the effect of social experiences outside of the drug context using isolation and aggression as experimental conditions. Studies comparing group-housed and single-housed rats have not been consistent. Thus, the reinforcing effect of cocaine has been reported to be increased both in isolated (Schenk et al., 1987; Boyle et al., 1991) and grouped (Hill and Powell, 1976; Morse et al., 1993; Phillips et al., 1994a,b) rats. Similar contradictory data can be found with amphetamine (ie, Bardo and Bevins, 2000 but Schenk et al., 1988), and results with morphine and heroin are weak (Alexander et al., 1978; Bozarth et al., 1989). Nevertheless, it seems that intake of ethanol and heroin is higher in isolated animals than social-housed animals (reviewed in Neisewander et al., 2012). Social aggression is achieved by the resident−intruder model in which brief agonistic confrontations occur between a nonaggressive rodent (ie, intruder) that is placed into the home cage of an aggressive rodent (ie, resident). In a series of papers, Miczek has shown that rats exposed to aggressive conspecifics have higher vulnerability to acquire cocaine self-administration relative to rats engaging in nonaggressive social encounters (Haney et al., 1995; Miczek and Mutschler, 1996; Tidey and Miczek, 1997; Kabbaj et al., 2001). Yet, it was suggested that the mechanism responsible for that has a psychological nature, rather than a simple physical (stress-induced blood corticosterone levels) nature (Covington and Miczek, 2005). Supporting this idea, increased intake of cocaine has also been reported in subordinated monkeys and rats forced to witness other rats receiving foot shock (Morgan et al., 2002; Czoty et al., 2005; Ramsey and Van Ree, 1993). Indeed, chronic subordination is stressful in both species (Blanchard et al., 2001; Nader et al., 2012), and results from several studies suggest that subordination stress causes dynamic regulatory changes in opiate systems that alter sensitivity to morphine reward (Neisewander et al., 2012).

The influence of isolation on vulnerability to drugs of abuse within the context in which the animals have access to drug is not clear, due to procedural difficulties. Thus, the findings from these studies are affected by several factors including strain, age, and length of isolation.

However, another set of experiments using social hierarchy as variable in rodents and monkeys suggests that subordination increases vulnerability for alcohol intake (Blanchard et al., 1992, 1987; Ellison, 1987; Ellison et al., 1983; Pohorecky, 2006, 2008, 2010). In mice, increases in ethanol intake are observed in subordinate, but not dominant, male C57BL/6 J mice (Kudryavtseva et al., 1991, 2006). Overall, this brief overview of emerging evidence suggest that the emotional valence of social circumstances and whether they occur within or outside of the drug-taking context is crucial on predisposing individuals to initiate on addictive behaviors.

Genetic Factors and Gene × Environment Interactions: A Focus on Alcoholism

Genetic Factors

For decades, researchers have tried to demonstrate genetic predispositions to addiction. To that end, several approaches have been used: studies demonstrating the role of heritable variation in addiction and the overlap across drugs; identification of putative candidate genes and results from genome-wide association studies, and novel research methods including endophenotypes, biomarkers, or imaging. However, linking particular genes with addictions has proved much more difficult. One of the reasons is the lack of replication of studies examining putative candidate genes for addiction-related phenotypes. Given this scenario, there are not that many genes that can be consistently associated with addiction, and they have been almost exclusively focused on alcohol and nicotine, and for most of the genes studied so far, there is merely some evidence (mainly for alcohol, nicotine, cannabis, cocaine, opioids, and more recently, gambling disorder) (reviewed in Agrawal et al., 2012). Let us have a closer look on alcohol, as due to the strongest genetic component it is probably the most researched among abused drugs. With regard to vulnerability for alcohol use disorders, human studies have also demonstrated a genetic component: first, the offspring of alcoholics have a 4−10-fold increased probability of developing alcoholism compared with the offspring of nonalcoholic parents (Mayfield et al., 2008), and second, from a meta-analysis performed with almost 10,000 monozygotic and dizygotic twin pairs, it has been shown that genetic influences are directly responsible for some of the individual differences observed in susceptibility to alcoholism, estimating the heritability of alcoholism to be around 50−60% (Goldman et al., 2005). From the 15

genome-wide association studies (GWAS) of alcohol use disorders and symptoms of alcohol use disorders, nine have been published and shown consistent results about gene clusters that encode products crucial for alcohol metabolism, such as alcohol dehydrogenase (ADH) (Rietchel and Trutelin, 2013; Frank et al., 2012; Biernacka et al., 2013).

From preclinical research, there is vast evidence showing the influence of genetic variations of neurotransmission in reward processing that in turn may affect characteristic behavior and susceptibility to addiction. Among them, endocannabinoid (Bilbao, 2013b), glutamatergic (Spanagel, 2003), and dopaminergic (Nutt et al., 2015) systems have been primary targets, and recent reports introduce novel neurotransmitters into the game, such dynorphins, orexins, histamine, gheralin, and galanin (Arias-Carrión and Salama, 2012). Coming back to alcohol, models using genetically modified animals have implicated numerous (>50) genes in not only alcohol reinforcement but the acquisition of alcohol consumption (Bilbao, 2013a). In this regard, a major hypothesis in the addiction field is that glutamatergic neurotransmission and neuroadaptive changes in glutamate receptors play a central role in alcoholism (Tsai et al., 1995; Krystal et al., 2003; Gass and Olive, 2008; Holmes et al., 2013). In particular, glutamatergic input onto the mesolimbic dopamine system appears to be relevant for the development of addictive behavior. The contribution of glutamate receptors in alcohol-related behaviors has been studied in either knockout mouse models or in pharmacological studies, and the results obtained point to a minor role of NMDA and AMPA receptors in alcohol reinforcement and alcohol-seeking responses (Sanchis-Segura et al., 2006; Spanagel, 2009; Bilbao, 2013a). However, relapse behavior, as measured by the ADE, is attenuated or blocked by several glutamate NMDA and AMPA receptor antagonists (Hölter et al., 1996; Vengeliene et al., 2005, 2008; Sanchis-Segura et al., 2006; Spanagel, 2009; Holmes et al., 2013). Thus, there is some indication that glutamate receptors are, at least in part, involved in mediating the addictive properties of alcohol, but the neuroanatomical substrates and the specific contributions of AMPA and NMDA receptors are not well understood. In a 2015 study, we demonstrated that dopamine and glutamatergic input act in concert to influence alcohol relapse responses using highly sophisticated mouse models, where particular glutamatergic genes were knocked out in two neuronal populations of the reward system (in simple words, the neurons receiving or triggering dopaminergic signal). In particular, we show that NMDA and AMPA receptor subunits within these neurons of the reward system play an important role in the ADE, the increase in alcohol intake after a period of abstinence. Thus, while initiation and maintenance of voluntary alcohol consumption in the home cage was not affected, the ADE was attenuated in all transgenic lines tested. Interestingly, the ability of conditioned cues to reinstate alcohol-seeking behavior was normal. Furthermore, we validated those finding by pharmacological manipulation of either NMDA or AMPA receptor activity in both neuronal populations. In conclusion, relapse-like drinking as measured by the ADE is mediated by NMDA and AMPA receptors within the mesolimbic system, whereas alcohol consumption, self-administration, and alcohol-seeking behavior—as measured by the context- and cue-induced reinstatement procedure—is not influenced by these mesolimbic glutamate receptors (Eisenhardt et al., 2015a).

Another interesting genetic component of alcohol (and natural reward-related behaviors) is the metabotropic glutamate receptor type 5 (mGluR5) and cannabinoid receptor CB1 interplay. Indeed, a crosstalk between these two receptors on mediating reward and reinforcement processes of drugs is illustrated by findings showing identical potency on modulating cue-induced reinstatement of drug-seeking responses (ie, Backstrom et al., 2004; Olive, 2009; Wang et al., 2012; De Vries et al., 2001; Sanchis-Segura et al., 2004; Cippitelli et al., 2005). More importantly, these two components are necessary for synaptic plasticity to occur. Thus, what is known is that both natural and drug reward-seeking processes depend on learning and the formation of long-lasting conditioned associations, and these learning processes may involve synaptic plasticity within the brain reward system, in particular of the NAc (ie, Stuber et al., 2011; Kelley, 2004; Todd et al., 2012; Crockford et al., 2005).

Alcohol seems to have a genetic component in the response to therapy. Indeed, it has been proposed that therapeutic responses to naltrexone in alcoholism are moderated by variation at the mu-opioid receptor gene locus. In a recent study, we examined in humanized mice carrying the respective human mu-opioid receptor (A118G) variations in the effects of naltrexone or nalmefene on brain stimulation and different paradigms of alcohol intake. It was found that one of these variations robustly moderated effects of opioid antagonism on alcohol reward and consumption, suggesting a personalized medicine approach to alcoholism treatment that takes into account the mu-opioid receptor gene genotype (Bilbao et al., 2015).

Gene × Environment Interactions

Addictive behavior, however, is not purely the result of an adverse combination of risk alleles. Today, it is believed from clinical and preclinical evidence that drug addiction is a multifactorial disorder in which genetic and environmental variables interact in modulating individual responsiveness to addictive drugs (Chen and Anthony, 2004). That is, addiction is the result of cumulative responses to drug exposure, the genetic and epigenetic

make-up of the individual, and environmental perturbations over time. Gene × environment interaction refers to moderation of genetic predisposition as a consequence of environmental exposure. In the past decades, from linkage and candidate gene studies and from the most modern GWAS, there has been an exponential increase in the number of gene × environment studies published (Dick et al., 2014). As for the genetic factors, an overview about specific interactions between different drugs of abuse, genes, and particular environments is beyond the scope here due to the vast research on this field. I will exemplify some of the work carried out in our lab by showing three specific interactions of alcohol with genes related to endocrine HPA axis activity and circadian control on the stress.

One important environmental factor that contributes to the development of alcohol use disorders is adverse life events (that is, stress). A representative example related to the stress HPA axis activity is that involving the CRH receptor 1 (Timpl et al., 1998). Spanagel showed in a science paper that mice lacking a functional CRH 1 receptor exposed to increasing concentrations of alcohol did not differ in their daily intake of alcohol or during the exposure to repeated episodes of social defeat stress. However, the knockout mice progressively started to increase their intake about 3 weeks later, an effect that persisted up to 6 months (Sillaber et al., 2002). Ten years later, using genetically modified mice with specific deletions of the CRH1 receptor either in the HPA or in the brain (in particular, the amygdala, a brain site that plays a key role in negative reinforcement processes in alcohol-dependent subjects), a second key paper showed that this delayed stress response in alcohol intake was indeed located in the HPA and not outside (or extrahypothalamic) (Molander et al., 2012). This particular interaction of HPA-CRH1-stress and the onset of alcoholism has been consistently demonstrated in human genetic studies as well (ie, Blomeyer et al., 2008). These results are in agreement with the suggested opposing roles of CRH1 receptors within the amygdala and the HPA axis (Heilig and Koob, 2007). Indeed, it is suggested that within the amygdale, CRH might interact with another neuropeptide, the neuropeptide Y to regulate responsiveness to stressful stimuli and alcohol-related behaviors (Heilig et al., 1994; Gilpin, 2012). Recently, several other stress-related neuropeptides have been identified that play a putative role in the regulation of alcohol consumption and relapse, including the urocortins, nociceptin, substance P, and neuropeptide S (Schank et al., 2012).

Another alcohol × stress × gene interaction is related to the internal clock. Alcohol consumption and corticosterone secretion are both under circadian control and display circadian rhythmicity. Consequently, the interactions between the circadian system, stress, and alcohol consumption are expected to occur too. Certainly, it is suggested that particular clock genes can control functions of the stress response system and that these interactions are affected by alcohol (Sarkar, 2012). A key study by Spanagel and colleagues in knockout mouse models revealed that the activity of the clock gene Per2 influenced alcohol consumption, a finding that was also supported by human genetic studies (Spanagel et al., 2005). Furthermore, it was later shown that genetic variation in the PER2 gene moderated the impact of severe life stress on hazardous drinking in experienced alcohol users (Blomeyer et al., 2013). This interaction seems to be bidirectional, as alcohol and stressors were reported to influence the expression of clock genes, and PER1 to be target gene for glucocorticoids in mice (Yamamoto et al., 2005) and humans (Reddy et al., 2009). In an additional work, we found an association between a functional genetic variaton in the promoter of the PER1 gene and increased alcohol drinking in adolescents exposed to severe adverse life events in early childhood (Dong et al., 2011). This functional genetic variation was involved in cortisol-induced, genotype-specific transcriptional activation of PER1. By knocking out the PER1 gene in mice, we could validate those results by applying various stressors such as social defeat stress and forced swim stress during voluntary alcohol home cage drinking to the Per1 knockout mice. Following these stressors, augmented stress-related drinking was observed in Per1 knockout mice as opposed to their wild type litter-mates (Dong et al., 2011). Another period gene, Per3 has an influence on responses to alcohol and stress, and it provides a potential causal link between stress, sleep disruption, and alcohol consumption (Wang et al., 2012).

In conclusion, what I have here briefly summarized reflects the complexity of the diversity in transition to addiction. That is, addiction is a multifaceted disorder heavily influenced among others, by gender, development, personality traits, psychiatric conditions, environmental-related drug association, social stress, and genetic factors. Although I have introduced them separately, their dynamic interactions, rather than single factors, will determine the course and severity of the addiction.

CONCLUDING REMARKS

- Throughout history, addiction has always been present in humans. During prehistoric times, the use substances influencing mood and thinking processes was restricted to particular environmental conditions and influenced by three dominant patterns of use: religious, medicinal, and recreational. In the 18th century, many substances sifted to a non-socially accepted pattern of abuse and dependence. The recognition of this new and pathological use led to an explosion in drug research that culminated in the development of the science of addiction.

Scientifically, drug addiction or substance dependence is a chronically relapsing disorder that is characterized by (1) compulsion to seek and take the drug, (2) loss of control in limiting intake, and (3) emergence of a negative emotional state, like anxiety or irritability, when access to the drug is prevented (defined as dependence). Addiction is further conceptualized as a progression from impulsivity to compulsivity, and it includes three stages: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation. Recent advances in neuroscience and clinical and public health have added new aspects and expanded the scientific definition of addiction. This is reflected in the new psychiatric classification system DSM-V, which has for the first time categorized drug addictions vs. so-called behavioral addictions and has added the addiction of gambling disorder. This new conceptualization marks a milestone in psychiatry and may open a new era of addiction in science where other potential behavioral addictions like sexual, internet, shopping, sports, or eating might be (scientifically) defined.

- The psychological constructs through which drugs modify gradually behavior during the transition to addiction depend on learning and the formation of long-lasting conditioned associations, and they include multiple motivational mechanisms. A central pillar from different approaches or theories aiming to explain the motivational/psychological mechanisms involved in the addiction process is based on reward dysregulation. The theory of counter-adaptation opponent-process and allostasis models proposes that chronic drug-induced states of anhedonia (as opposing to the acute, positive effects) represent one of the major motivations for compulsivity in drug taking in the form of a motivational withdrawal syndrome. The incentive sensitization theory proposes that repeated drug use sensitizes neuronal circuits that mediate psychostimulant motor effects, drug reward, and the attribution of incentive salience to reward-associated environmental cues. This shift in an incentive salience state is responsible for drug-seeking and drug-taking behavior. From the transition to habit theory, a switch from a reward-sensitive behavior to a habit-based behavior is proposed to underlie decreased reward sensitivity. Consequently, the seeking behavior will be triggered by a stimulus–response habit and the habit (and not the affective reward response) will be critical in maintaining the addictive behavior. Finally, the impulsivity models proposed that prolonged drug intake affects impulse control mechanisms that may lead to addictive behaviors. The reward system provides the anatomical substrate for emotions and motivated behavior, including the circuitry for reward-related events. Compared to natural rewards, drugs of abuse impact this system differently, so the addicted brain programs behavior differently. The functional consequences of chronic, long-term exposure to addictive drugs believed to underlie addiction are mainly the development of tolerance, sensitization, and dependence. The neuropsychological adaptations of dependence, craving, and relapse to drugs in humans involves progressive new programming of neural circuits that mediate reward and motivation, memory, conditioning, and habituation processes, executive function and inhibitory control, interoception, and self-awareness and stress reactivity.
- To understand the complexity of addiction is fundamental to elucidate how rewards and reinforcement processes impact the addictive behavior and which are the relevant behavioral hallmarks of addiction. The most common methods used to measure reward in humans include acute dose-effect comparison, self-reports, subject ratings of estimates of street value, self-administration, and the more objective choice procedure; the recent behavioral economics approach applied to addiction has the main advantage of the direct comparison between qualitatively different reinforcers by means of delay-discounting. Among the measurements of reward in humans, "craving" is most probably the one that has attracted more attention as a core component of drug abuse. However, modeling relapse situations and compulsive drug seeking in laboratory settings remains a challenge in the field of human research. Both reward-induced motivational processes and some of the key symptoms of addictive behavior can be reproduced in animals, and therefore they can be used to study the psychobiological mechanisms underlying addiction in humans. Thus, the motivational properties of rewards are evaluated through consumption/preference-based measures, which include self-administration, conditioning place preference, and brain self-stimulation paradigms. Currently, it is possible to model at least some of the features that characterize the transition to addiction in humans. These addictive phenotypes include increased motivation for drugs, drug seeking, relapse, loss of control, and intake despite negative consequences. Importantly, the three-criteria addiction model for cocaine represents an exceptional model developed in the last few years that best captures addictive behavior as a whole in rats.
- Preclinical and clinical evidence has extensively reported that the transition to addiction is heavily influenced by biological, personality, environmental, and genetic factors and their dynamic interactions, which will determine the course and severity of the addiction. The most influencing biological and developmental factors include gender and adolescence. The general pattern of gender differences is pretty similar for all drugs of abuse and stages of addiction, with females being more susceptible, an effect suggested to be

mediated by emotional and neuroendocrine processes. Adolescence is a crucial time for the development of drug use and addiction. An immature brain more sensitive to drugs and psychological traits like risk behavior that favors a reward approach are key factors that contribute to it. Individuals with preexisting psychological and emotional disorders including anxiety, novelty seeking, and impulsivity are among the most predisposing personality traits and psychiatric conditions to addiction. Mostly from preclinical evidence, it is known that the environment can affect addictive behaviors by means of adverse life experiences, enhanced drug-associated learning, and the setting associated to drug taking; interestingly, there is emerging interest on how the individual social environment impacts addictive behavior, particularly the emotional valence of the social experience and the context in which the social interaction occurs, within or outside of the drug-taking context. Linking particular genes with addictions has proved difficult due to the lack of replication studies. Alcoholism might be an exception, as it has been the most researched addiction due to its strong genetic component. Thus, the offspring of alcoholics have a 4−10-fold increased probability of developing alcoholism, the heritability of alcoholism is estimated to be around 50−60%, and the genetic variations of ADH has proven to be crucial. An extensive animal research has demonstrated an important role for genes related to the glutamate and opioid systems in alcohol relapse and in response to therapy, respectively. More importantly, genetic and environmental variables interact in modulating individual responsiveness to addictive drugs. In particular, both the HPA stress axis and circadian genes seem to modulate stress-related alcohol responses.

REFERENCES

Abdolahi, A., Acosta, G., Breslin, F.J., Hemby, S.E., Lynch, W.J., 2010. Incubation of nicotine seeking is associated with enhanced protein kinase A-regulated signaling of dopamine- and cAMP-regulated phosphoprotein of 32 kDa in the insular cortex. European Journal of Neuroscience 31, 733−741.

Agrawal, A., Verweij, K.J., Gillespie, N.A., Heath, A.C., Lessov-Schlaggar, C.N., Martin, N.G., Nelson, E.C., Slutske, W.S., Whitfield, J.B., Lynskey, M.T., 2012. The genetics of addiction-a translational perspective. Translational Psychiatry 2, e140.

Aharonovich, E., Hasin, D.S., Brooks, A.C., Liu, X., Bisaga, A., Nunes, E.V., 2006. Cognitive deficits predict low treatment retention in cocaine dependent patients. Drug and Alcohol Dependence 81, 313−322.

Ahmed, S.H., Koob, G.F., 1998. Transition from moderate to excessive drug intake: change in hedonic set point. Science 282, 298−300.

Ahmed, S.H., 2011. Escalation of drug use. Animal models of drug addiction. Neuromethods 267−292.

Alexander, B.K., Coambs, R.B., Hadaway, P.F., 1978. The effect of housing and gender on morphine self-administration in rats. Psychopharmacology (Berlin) 58, 175−179.

Aloise-Young, P.A., Kaeppner, C.J., 2005. Sociometric status as a predictor of onset and progression in adolescent cigarette smoking. Nicotine and Tobacco Research 7, 199−206.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, fourth ed. American PsychiatricPress, Washington D.C.

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, fifth ed. American PsychiatricPublishing, Arlington.

Andersen, S.L., Napierata, L., Brenhouse, H.C., Sonntag, K.C., 2008. Juvenile methylphenidate modulates reward-related behaviors and cerebral blood flow by decreasing cortical D3 receptors. European Journal of Neuroscience 27, 2962−2972.

Anisman, H., Waller, T.G., 1974. Effects of inescapable shock and shock-produced conflict on self selection of alcohol in rats. Pharmacology Biochemistry and Behavior 2, 27−33.

Anker, J.J., Carroll, M.E., 2010. The role of progestins in the behavioral effects of cocaine and other drugs of abuse: human and animal research. Neuroscience and Biobehavioral Reviews 35, 315−333.

Anker, J.J., Perry, J.L., Gliddon, L.A., Carroll, M.E., 2009. Impulsivity predicts the escalation of cocaine self-administration in rats. Pharmacology Biochemistry and Behavior 93, 343−348.

Arias-Carrion, O., Salama, M., 2012. Reward-seeking behavior and addiction: cause or cog? Current Drug Abuse Reviews 5, 178−189.

Astur, R.S., Carew, A.W., Deaton, B.E., 2014. Conditioned place preferences in humans using virtual reality. Behavioural Brain Research 267, 173−177.

Astur, R.S., Palmisano, A.N., Carew, A.W., Deaton, B.E., Kuhney, F.S., Niezrecki, R.N., Hudd, E.C., Mendicino, K.L., Ritter, C.J., 2016. Conditioned place preferences in humans using secondary reinforcers. Behavioural Brain Research 297, 15−19.

Baarendse, P.J., Limpens, J.H., Vanderschuren, L.J., 2014. Disrupted social development enhances the motivation for cocaine in rats. Psychopharmacology (Berlin) 231, 1695−1704.

Bachteler, D., Economidou, D., Danysz, W., Ciccocioppo, R., Spanagel, R., 2005. The effects of acamprosate and neramexane on cue-induced reinstatement of ethanol-seeking behavior in rat. Neuropsychopharmacology 30, 1104−1110.

Backstrom, P., Bachteler, D., Koch, S., Hyytia, P., Spanagel, R., 2004. mGluR5 antagonist MPEP reduces ethanol-seeking and relapse behavior. Neuropsychopharmacology 29, 921−928.

Badanich, K.A., Adler, K.J., Kirstein, C.L., 2006. Adolescents differ from adults in cocaine conditioned place preference and cocaine-induced dopamine in the nucleus accumbens septi. European Journal of Pharmacology 550, 95−106.

Badiani, A., Spagnolo, P.A., 2013. Role of environmental factors in cocaine addiction. Current Pharmaceutical Design 19, 6996−7008.

Baez, H., Castro, M.M., Benavente, M.A., Kintz, P., Cirimele, V., Camargo, C., Thomas, C., 2000. Drugs in prehistory: chemical analysis of ancient human hair. Forensic Science International 108, 173−179.

Bahi, A., 2013. Individual differences in elevated plus-maze exploration predicted higher ethanol consumption and preference in outbred mice. Pharmacology Biochemistry and Behavior 105, 83−88.

Bardo, M.T., Bevins, R.A., 2000. Conditioned place preference: what does it add to our preclinical understanding of drug reward? Psychopharmacology (Berlin) 153, 31–43.

Baumeister, R.F., Stillwell, A.M., Heatherton, T.F., 1994. Guilt: an interpersonal approach. Psychological Bulletin 115, 243–267.

Becker, J.B., Hu, M., 2008. Sex differences in drug abuse. Frontiers in Neuroendocrinology 29, 36–47.

Becker, J.B., Koob, G.F., 2016. Sex differences in animal models: focus on addiction. Pharmacological Reviews 68, 242–263.

Becker, H.C., Lopez, M.F., Doremus-Fitzwater, T.L., 2011. Effects of stress on alcohol drinking: a review of animal studies. Psychopharmacology (Berlin) 218, 131–156.

Belin, D., Mar, A.C., Dalley, J.W., Robbins, T.W., Everitt, B.J., 2008. High impulsivity predicts the switch to compulsive cocaine-taking. Science 320, 1352–1355.

Belin, D., Balado, E., Piazza, P.V., Deroche-Gamonet, V., 2009. Pattern of intake and drug craving predict the development of cocaine addiction-like behavior in rats. Biological Psychiatry 65, 863–868.

Belin, D., Berson, N., Balado, E., Piazza, P.V., Deroche-Gamonet, V., 2011. High-novelty-preference rats are predisposed to compulsive cocaine self-administration. Neuropsychopharmacology 36, 569–579.

Belin, D., Belin-Rauscent, A., Murray, J.E., Everitt, B.J., 2013. Addiction: failure of control over maladaptive incentive habits. Current Opinion in Neurobiology 23, 564–572.

Ben-Shahar, O., Posthumus, E.J., Waldroup, S.A., Ettenberg, A., 2008. Heightened drug-seeking motivation following extended daily access to self-administered cocaine. Progress in Neuropsychopharmacology and Biological Psychiatry 32, 863–869.

Bianchi, M., Fone, K.F., Azmi, N., Heidbreder, C.A., Hagan, J.J., Marsden, C.A., 2006. Isolation rearing induces recognition memory deficits accompanied by cytoskeletal alterations in rat hippocampus. European Journal of Neuroscience 24, 2894–2902.

Bienkowski, P., Koros, E., Kostowski, W., 2001. Novelty-seeking behaviour and operant oral ethanol self-administration in Wistar rats. Alcohol and Alcoholism 36, 525–528.

Bienkowski, P., Rogowski, A., Korkosz, A., Mierzejewski, P., Radwanska, K., Kaczmarek, L., Bogucka-Bonikowska, A., Kostowski, W., 2004. Time-dependent changes in alcohol-seeking behaviour during abstinence. European Neuropsychopharmacology 14, 355–360.

Biernacka, J.M., Geske, J.R., Schneekloth, T.D., Frye, M.A., Cunningham, J.M., Choi, D.S., Tapp, C.L., Lewis, B.R., Drews, M.S., L Pietrzak, T., Colby, C.L., Hall-Flavin, D.K., Loukianova, L.L., Heit, J.A., Mrazek, D.A., Karpyak, V.M., 2013. Replication of genome wide association studies of alcohol dependence: support for association with variation in ADH1C. PLoS One 8 (3), e58798.

Bilbao, A., Robinson, J.E., Heilig, M., Malanga, C.J., Spanagel, R., Sommer, W.H., Thorsell, A., 2015. A pharmacogenetic determinant of mu-opioid receptor antagonist effects on alcohol reward and consumption: evidence from humanized mice. Biological Psychiatry 77, 850–858.

Bilbao, A., 2013a. Advanced transgenic approaches to understand alcohol-related phenotypes in animals. Current Topics in Behavioral Neurosciences 13, 271–311.

Bilbao, A., 2013b. The role of the endocannabinoid system in addictive behavior. Addiction Biology 18, 904–907.

Bisagno, V., Cadet, J.L., 2014. Stress, sex, and addiction: potential roles of corticotropin-releasing factor, oxytocin, and arginine-vasopressin. Behavioural Pharmacology 25, 445–457.

Bishop, M.P., Elder, S.T., Heath, R.G., 1963. Intracranial self-stimulation in man. Science 140, 394–396.

Blanchard, R.J., Hori, K., Tom, P., Blanchard, D.C., 1987. Social structure and ethanol consumption in the laboratory rat. Pharmacology Biochemistry and Behavior 28, 437–442.

Blanchard, R.J., Flores, T., Magee, L., Weiss, S., Blanchard, D.C., 1992. Pregrouping aggression and defense scores influences alcohol consumption for dominant and subordinate rats in visible burrow systems. Aggressive Behavior 18, 459–467.

Blanchard, R.J., McKittrick, C.R., Blanchard, D.C., 2001. Animal models of social stress: effects on behavior and brain neurochemical systems. Physiology and Behavior 73, 261–271.

Blatt, S.L., Takahashi, R.N., 1999. Experimental anxiety and the reinforcing effects of ethanol in rats. Brazilian Journal of Medical and Biological Research 32, 457–461.

Blomeyer, D., Treutlein, J., Esser, G., Schmidt, M.H., Schumann, G., Laucht, M., 2008. Interaction between CRHR1 gene and stressful life events predicts adolescent heavy alcohol use. Biological Psychiatry 63, 146–151.

Blomeyer, D., Buchmann, A.F., Lascorz, J., Zimmermann, U.S., Esser, G., Desrivieres, S., Schmidt, M.H., Banaschewski, T., Schumann, G., Laucht, M., 2013. Association of PER2 genotype and stressful life events with alcohol drinking in young adults. PLoS One 8, e59136.

Blum, K., Sheridan, P.J., Wood, R.C., Braverman, E.R., Chen, T.J., Cull, J.G., Comings, D.E., 1996. The D2 dopamine receptor gene as a determinant of reward deficiency syndrome. Journal of the Royal Society of Medicine 89, 396–400.

Bolla, K.I., Eldreth, D.A., London, E.D., Kiehl, K.A., Mouratidis, M., Contoreggi, C., Matochik, J.A., Kurian, V., Cadet, J.L., Kimes, A.S., Funderburk, F.R., Ernst, M., 2003. Orbitofrontal cortex dysfunction in abstinent cocaine abusers performing a decision-making task. Neuroimage 19, 1085–1094.

Bossert, J.M., Marchant, N.J., Calu, D.J., Shaham, Y., 2013. The reinstatement model of drug relapse: recent neurobiological findings, emerging research topics, and translational research. Psychopharmacology (Berlin) 229, 453–476.

Boyle, A.E., Gill, K., Smith, B.R., Amit, Z., 1991. Differential effects of an early housing manipulation on cocaine-induced activity and self-administration in laboratory rats. Pharmacology Biochemistry and Behavior 39, 269–274.

Bozarth, M.A., Murray, A., Wise, R.A., 1989. Influence of housing conditions on the acquisition of intravenous heroin and cocaine self-administration in rats. Pharmacology Biochemistry and Behavior 33, 903–907.

Braams, B.R., van Duijvenvoorde, A.C., Peper, J.S., Crone, E.A., 2015. Longitudinal changes in adolescent risk-taking: a comprehensive study of neural responses to rewards, pubertal development, and risk-taking behavior. Journal of Neuroscience 35, 7226–7238.

Brady, K.T., Randall, C.L., 1999. Gender differences in substance use disorders. Psychiatric Clinics of North America 22, 241–252.

Brady, K.T., Sinha, R., 2005. Co-occurring mental and substance use disorders: the neurobiological effects of chronic stress. American Journal of Psychiatry 162, 1483–1493.

Brenhouse, H.C., Sonntag, K.C., Andersen, S.L., 2008. Transient D1 dopamine receptor expression on prefrontal cortex projection neurons: relationship to enhanced motivational salience of drug cues in adolescence. Journal of Neuroscience 28, 2375–2382.

Briand, L.A., Flagel, S.B., Garcia-Fuster, M.J., Watson, S.J., Akil, H., Sarter, M., Robinson, T.E., 2008. Persistent alterations in cognitive function and prefrontal dopamine D2 receptors following extended,

but not limited, access to self-administered cocaine. Neuropsychopharmacology 33, 2969–2980.

Caine, S.B., Lintz, R., Koob, G.F., 1993. Intravenous drug self-administration techniques in animals. In: Behavioral Neuroscience: A Practical Approach, vol. 2. IRL Press, Oxford, pp. 117–143.

Caprioli, D., Celentano, M., Paolone, G., Badiani, A., 2007. Modeling the role of environment in addiction. Progress in Neuropsychopharmacology and Biological Psychiatry 31, 1639–1653.

Caprioli, D., Celentano, M., Dubla, A., Lucantonio, F., Nencini, P., Badiani, A., 2009. Ambience and drug choice: cocaine- and heroin-taking as a function of environmental context in humans and rats. Biological Psychiatry 65, 893–899.

Carlezon Jr., W.A., Chartoff, E.H., 2007. Intracranial self-stimulation (ICSS) in rodents to study the neurobiology of motivation. Nature Protocols 2, 2987–2995.

Carroll, M.E., Lynch, W.J., Roth, M.E., Morgan, A.D., Cosgrove, K.P., 2004. Sex and estrogen influence drug abuse. Trends in Pharmacological Sciences 25, 273–279.

Carter, B.L., Tiffany, S.T., 1999. Cue-reactivity and the future of addiction research. Addiction 94, 349–351.

Cartmell, L.W., Aufderhide, A., Weems, C., 1991. Cocaine metabolites in pre-Columbian mummy hair. Journal of Oklahoma State Medical Association 84, 11–12.

Casey, B.J., Jones, R.M., 2010. Neurobiology of the adolescent brain and behavior: implications for substance use disorders. Journal of the American Academy of Child and Adolescent Psychiatry 49, 1189–1201 quiz 1285.

Celentano, M., Caprioli, D., Dipasquale, P., Cardillo, V., Nencini, P., Gaetani, S., Badiani, A., 2009. Drug context differently regulates cocaine versus heroin self-administration and cocaine- versus heroin-induced Fos mRNA expression in the rat. Psychopharmacology (Berlin) 204, 349–360.

Chen, C.Y., Anthony, J.C., 2004. Epidemiological estimates of risk in the process of becoming dependent upon cocaine: cocaine hydrochloride powder versus crack cocaine. Psychopharmacology (Berlin) 172, 78–86.

Childers, S.R., Breivogel, C.S., 1998. Cannabis and endogenous cannabinoid systems. Drug and Alcohol Dependence 51, 173–187.

Childress, A.R., McLellan, A.T., O'Brien, C.P., 1984. Assessment and extinction of conditioned withdrawal-like responses in an integrated treatment for opiate dependence. NIDA Research Monographs 55, 202–210.

Childress, A.R., McLellan, A.T., O'Brien, C.P., 1986. Abstinent opiate abusers exhibit conditioned craving, conditioned withdrawal and reductions in both through extinction. British Journal of Addiction 81, 655–660.

Childress, A.R., McLellan, A.T., Ehrman, R., O'Brien, C.P., 1988. Classically conditioned responses in opioid and cocaine dependence: a role in relapse? NIDA Research Monographs 84, 25–43.

Childress, A.R., Mozley, P.D., McElgin, W., Fitzgerald, J., Reivich, M., O'Brien, C.P., 1999. Limbic activation during cue-induced cocaine craving. American Journal of Psychiatry 156, 11–18.

Childs, E., de Wit, H., 2009. Amphetamine-induced place preference in humans. Biological Psychiatry 65, 900–904.

Chung, T., Martin, C.S., 2001. Classification and course of alcohol problems among adolescents in addictions treatment programs. Alcoholism: Clinical and Experimental Research 25, 1734–1742.

Ciccocioppo, R., Economidou, D., Cippitelli, A., Cucculelli, M., Ubaldi, M., Soverchia, L., Lourdusamy, A., Massi, M., 2006. Genetically selected Marchigian Sardinian alcohol-preferring (msP) rats: an animal model to study the neurobiology of alcoholism. Addiction Biology 11, 339–355.

Cippitelli, A., Bilbao, A., Hansson, A.C., del Arco, I., Sommer, W., Heilig, M., Massi, M., Bermudez-Silva, F.J., Navarro, M., Ciccocioppo, R., de Fonseca, F.R., European, T.C., 2005. Cannabinoid CB1 receptor antagonism reduces conditioned reinstatement of ethanol-seeking behavior in rats. European Journal of Neuroscience 21, 2243–2251.

Cloninger, C.R., Svrakic, D.M., Przybeck, T.R., 1993. A psychobiological model of temperament and character. Archives of General Psychiatry 50, 975–990.

Cloninger, C.R., 1987. Neurogenetic adaptive mechanisms in alcoholism. Science 236, 410–416.

Colombo, G., Lobina, C., Carai, M.A., Gessa, G.L., 2006. Phenotypic characterization of genetically selected Sardinian alcohol-preferring (sP) and -non-preferring (sNP) rats. Addiction Biology 11, 324–338.

Comer, S.D., Ashworth, J.B., Foltin, R.W., Johanson, C.E., Zacny, J.P., Walsh, S.L., 2008. The role of human drug self-administration procedures in the development of medications. Drug and Alcohol Dependence 96, 1–15.

Conger, J.J., 1956. Alcoholism: theory, problem and challenge. II. Reinforcement theory and the dynamics of alcoholism. Quarterly Journal of Studies on Alcohol 17, 296–305.

Cooper, Z.D., Haney, M., 2014. Investigation of sex-dependent effects of cannabis in daily cannabis smokers. Drug and Alcohol Dependence 136, 85–91.

Corbit, L.H., Nie, H., Janak, P.H., 2012. Habitual alcohol seeking: time course and the contribution of subregions of the dorsal striatum. Biological Psychiatry 72, 389–395.

Covington 3rd, H.E., Miczek, K.A., 2005. Intense cocaine self-administration after episodic social defeat stress, but not after aggressive behavior: dissociation from corticosterone activation. Psychopharmacology (Berlin) 183, 331–340.

Crockford, D.N., Goodyear, B., Edwards, J., Quickfall, J., el-Guebaly, N., 2005. Cue-induced brain activity in pathological gamblers. Biological Psychiatry 58, 787–795.

Crocq, M.A., 2007. Historical and cultural aspects of man's relationship with addictive drugs. Dialogues in Clinical Neuroscience 9, 355–361.

Cunningham, K.A., Anastasio, N.C., 2014. Serotonin at the nexus of impulsivity and cue reactivity in cocaine addiction. Neuropharmacology 76 (Pt B), 460–478.

Cunningham, J.A., 2000. Remissions from drug dependence: is treatment a prerequisite? Drug and Alcohol Dependence 59, 211–213.

Czoty, P.W., McCabe, C., Nader, M.A., 2005. Assessment of the relative reinforcing strength of cocaine in socially housed monkeys using a choice procedure. Journal of Pharmacology and Experimental Therapeutics 312, 96–102.

Dalley, J.W., Theobald, D.E., Pereira, E.A., Li, P.M., Robbins, T.W., 2002. Specific abnormalities in serotonin release in the prefrontal cortex of isolation-reared rats measured during behavioural performance of a task assessing visuospatial attention and impulsivity. Psychopharmacology (Berlin) 164, 329–340.

Dalley, J.W., Laane, K., Pena, Y., Theobald, D.E., Everitt, B.J., Robbins, T.W., 2005a. Attentional and motivational deficits in rats withdrawn from intravenous self-administration of cocaine or heroin. Psychopharmacology (Berlin) 182, 579–587.

Dalley, J.W., Theobald, D.E., Berry, D., Milstein, J.A., Laane, K., Everitt, B.J., Robbins, T.W., 2005b. Cognitive sequelae of intravenous amphetamine self-administration in rats: evidence for selective effects on attentional performance. Neuropsychopharmacology 30, 525–537.

Dalley, J.W., Laane, K., Theobald, D.E., Pena, Y., Bruce, C.C., Huszar, A.C., Wojcieszek, M., Everitt, B.J., Robbins, T.W., 2007. Enduring deficits in sustained visual attention during withdrawal of intravenous methylenedioxymethamphetamine self-administration in rats: results from a comparative study with d-amphetamine and methamphetamine. Neuropsychopharmacology 32, 1195–1206.

Dalley, J.W., Mar, A.C., Economidou, D., Robbins, T.W., 2008. Neurobehavioral mechanisms of impulsivity: fronto-striatal systems and functional neurochemistry. Pharmacology Biochemistry and Behavior 90, 250–260.

De Vries, T.J., Shaham, Y., Homberg, J.R., Crombag, H., Schuurman, K., Dieben, J., Vanderschuren, L.J., Schoffelmeer, A.N., 2001. A cannabinoid mechanism in relapse to cocaine seeking. Nature Medicine 7, 1151–1154.

de Wit, H., Chutuape, M.A., 1993. Increased ethanol choice in social drinkers following ethanol preload. Behavioural Pharmacology 4, 29–36.

dela Pena, I., Gonzales, E.L., de la Pena, J.B., Kim, B.N., Han, D.H., Shin, C.Y., Cheong, J.H., 2015. Individual differences in novelty-seeking behavior in spontaneously hypertensive rats: enhanced sensitivity to the reinforcing effect of methylphenidate in the high novelty-preferring subpopulation. Journal of Neuroscience Methods 252, 48–54.

Deroche-Gamonet, V., Belin, D., Piazza, P.V., 2004. Evidence for addiction-like behavior in the rat. Science 305, 1014–1017.

Di Paolo, T., Falardeau, P., Morissette, M., 1988. Striatal D-2 dopamine agonist binding sites fluctuate during the rat estrous cycle. Life Sciences 43, 665–672.

Dick, D.M., Cho, S.B., Latendresse, S.J., Aliev, F., Nurnberger Jr., J.I., Edenberg, H.J., Schuckit, M., Hesselbrock, V.M., Porjesz, B., Bucholz, K., Wang, J.C., Goate, A., Kramer, J.R., Kuperman, S., 2014. Genetic influences on alcohol use across stages of development: GABRA2 and longitudinal trajectories of drunkenness from adolescence to young adulthood. Addiction Biology 19, 1055–1064.

Dickinson, A., Wood, N., Smith, J.W., 2002. Alcohol seeking by rats: action or habit? Quarterly Journal of Experimental Psychology B 55, 331–348.

Diergaarde, L., Pattij, T., Poortvliet, I., Hogenboom, F., de Vries, W., Schoffelmeer, A.N., De Vries, T.J., 2008. Impulsive choice and impulsive action predict vulnerability to distinct stages of nicotine seeking in rats. Biological Psychiatry 63, 301–308.

Diergaarde, L., Pattij, T., Nawijn, L., Schoffelmeer, A.N., De Vries, T.J., 2009. Trait impulsivity predicts escalation of sucrose seeking and hypersensitivity to sucrose-associated stimuli. Behavioral Neuroscience 123, 794–803.

Dilleen, R., Pelloux, Y., Mar, A.C., Molander, A., Robbins, T.W., Everitt, B.J., Dalley, J.W., Belin, D., 2012. High anxiety is a predisposing endophenotype for loss of control over cocaine, but not heroin, self-administration in rats. Psychopharmacology (Berlin) 222, 89–97.

Dong, L., Bilbao, A., Laucht, M., Henriksson, R., Yakovleva, T., Ridinger, M., Desrivieres, S., Clarke, T.K., Lourdusamy, A., Smolka, M.N., Cichon, S., Blomeyer, D., Treutlein, J., Perreau-Lenz, S., Witt, S., Leonardi-Essmann, F., Wodarz, N., Zill, P., Soyka, M., Albrecht, U., Rietschel, M., Lathrop, M., Bakalkin, G., Spanagel, R., Schumann, G., 2011. Effects of the circadian rhythm gene period 1 (per1) on psychosocial stress-induced alcohol drinking. American Journal of Psychiatry 168, 1090–1098.

Duncan, E., Boshoven, W., Harenski, K., Fiallos, A., Tracy, H., Jovanovic, T., Hu, X., Drexler, K., Kilts, C., 2007. An fMRI study of the interaction of stress and cocaine cues on cocaine craving in cocaine-dependent men. American Journal of Addictions 16, 174–182.

Eaton, D.K., Kann, L., Kinchen, S., Shanklin, S., Flint, K.H., Hawkins, J., Harris, W.A., Lowry, R., McManus, T., Chyen, D., Whittle, L., Lim, C., Wechsler, H., Centers for Disease (CDC), 2012. Youth risk behavior surveillance – United States, 2011. MMWR Surveillance Summaries 61, 1–162.

Ebel, R.L., 1961. Must all tests be valid? American Psychologist 16, 640–647.

Economidou, D., Pelloux, Y., Robbins, T.W., Dalley, J.W., Everitt, B.J., 2009. High impulsivity predicts relapse to cocaine-seeking after punishment-induced abstinence. Biological Psychiatry 65, 851–856.

Eisenhardt, M., Leixner, S., Lujan, R., Spanagel, R., Bilbao, A., 2015a. Glutamate receptors within the mesolimbic dopamine system mediate alcohol relapse behavior. Journal of Neuroscience 35, 15523–15538.

Eisenhardt, M., Leixner, S., Spanagel, R., Bilbao, A., 2015b. Quantification of alcohol drinking patterns in mice. Addiction Biology 20, 1001–1011.

Ellison, G., Levy, A., Lorant, N., 1983. Alcohol-preferring rats in colonies show withdrawal, inactivity, and lowered dominance. Pharmacology Biochemistry and Behavior 18 (Suppl. 1), 565–570.

Ellison, G., 1987. Stress and alcohol intake: the socio-pharmacological approach. Physiology and Behavior 40, 387–392.

Epstein, L.H., Bulik, C.M., Perkins, K.A., Caggiula, A.R., Rodefer, J., 1991. Behavioral economic analysis of smoking: money and food as alternatives. Pharmacology Biochemistry and Behavior 38, 715–721.

Ernst, M., Luciana, M., 2015. Neuroimaging of the dopamine/reward system in adolescent drug use. CNS Spectrums 20, 427–441.

Ersche, K.D., Jones, P.S., Williams, G.B., Turton, A.J., Robbins, T.W., Bullmore, E.T., 2012a. Abnormal brain structure implicated in stimulant drug addiction. Science 335, 601–604.

Ersche, K.D., Turton, A.J., Chamberlain, S.R., Muller, U., Bullmore, E.T., Robbins, T.W., 2012b. Cognitive dysfunction and anxious-impulsive personality traits are endophenotypes for drug dependence. American Journal of Psychiatry 169, 926–936.

Evans, S.M., Haney, M., Foltin, R.W., 2002. The effects of smoked cocaine during the follicular and luteal phases of the menstrual cycle in women. Psychopharmacology (Berlin) 159, 397–406.

Everitt, B.J., Robbins, T.W., 2005. Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nature Neuroscience 8, 1481–1489.

Everitt, B.J., Wolf, M.E., 2002. Psychomotor stimulant addiction: a neural systems perspective. Journal of Neuroscience 22, 3312–3320.

Everitt, B.J., Dickinson, A., Robbins, T.W., 2001. The neuropsychological basis of addictive behaviour. Brain Research. Brain Research Reviews 36, 129–138.

Everitt, B.J., Belin, D., Economidou, D., Pelloux, Y., Dalley, J.W., Robbins, T.W., 2008. Review. Neural mechanisms underlying the vulnerability to develop compulsive drug-seeking habits and

addiction. Philosophical Transactions of the Royal Society London B: Biological Sciences 363, 3125–3135.

Fernandez-Ruiz, J.J., de Miguel, R., Hernandez, M.L., Ramos, J.A., 1990. Time-course of the effects of ovarian steroids on the activity of limbic and striatal dopaminergic neurons in female rat brain. Pharmacology Biochemistry and Behavior 36, 603–606.

Fillmore, M.I., Rush, C.R., 2001. Alcohol effects on inhibitory and activational response strategies in the acquisition of alcohol and other reinforcers: priming the motivation to drink. Journal of Studies on Alcohol 62, 646–656.

Foltin, R.W., Fischman, M.W., 1991. Assessment of abuse liability of stimulant drugs in humans: a methodological survey. Drug and Alcohol Dependence 28, 3–48.

Fone, K.C., Porkess, M.V., 2008. Behavioural and neurochemical effects of post-weaning social isolation in rodents-relevance to developmental neuropsychiatric disorders. Neuroscience and Biobehavioral Reviews 32, 1087–1102.

Frank, J., Cichon, S., Treutlein, J., Ridinger, M., Mattheisen, M., Hoffmann, P., Herms, S., Wodarz, N., Soyka, M., Zill, P., Maier, W., Mossner, R., Gaebel, W., Dahmen, N., Scherbaum, N., Schmal, C., Steffens, M., Lucae, S., Ising, M., Muller-Myhsok, B., Nothen, M.M., Mann, K., Kiefer, F., Rietschel, M., 2012. Genome-wide significant association between alcohol dependence and a variant in the ADH gene cluster. Addiction Biology 17, 171–180.

Franken, I.H., van de Wetering, B.J., 2015. Bridging the gap between the neurocognitive lab and the addiction clinic. Addictive Behaviors 44, 108–114.

Galli, G., Wolffgramm, J., 2011. Long-term development of excessive and inflexible nicotine taking by rats, effects of a novel treatment approach. Behavioural Brain Research 217, 261–270.

Gallop, R.J., Crits-Christoph, P., Ten Have, T.R., Barber, J.P., Frank, A., Griffin, M.L., Thase, M.E., 2007. Differential transitions between cocaine use and abstinence for men and women. Journal of Consulting and Clinical Psychology 75, 95–103.

Gass, J.T., Olive, M.F., 2008. Glutamatergic substrates of drug addiction and alcoholism. Biochemical Pharmacology 75, 218–265.

Gawin, F., Kleber, H., 1986. Pharmacologic treatments of cocaine abuse. Psychiatric Clinics of North America 9, 573–583.

Giancola, P.R., Moss, H.B., Martin, C.S., Kirisci, L., Tarter, R.E., 1996. Executive cognitive functioning predicts reactive aggression in boys at high risk for substance abuse: a prospective study. Alcoholism: Clinical and Experimental Research 20, 740–744.

Gilpin, N.W., 2012. Corticotropin-releasing factor (CRF) and neuropeptide Y (NPY): effects on inhibitory transmission in central amygdala, and anxiety- & alcohol-related behaviors. Alcohol 46, 329–337.

Goeders, N.E., Guerin, G.F., 1994. Non-contingent electric footshock facilitates the acquisition of intravenous cocaine self-administration in rats. Psychopharmacology (Berlin) 114, 63–70.

Goeders, N.E., 2002. Stress and cocaine addiction. Journal of Pharmacology and Experimental Therapeutics 301, 785–789.

Goldman, D., Oroszi, G., Ducci, F., 2005. The genetics of addictions: uncovering the genes. Nature Reviews Genetics 6, 521–532.

Goto, Y., Otani, S., Grace, A.A., 2007. The Yin and Yang of dopamine release: a new perspective. Neuropharmacology 53, 583–587.

Grant, J.E., 2008. Impulse Control Disorders. A Clinician's Guide to Understanding and Treating Behavioral Addictions, first ed. W.W. Norton & Company, New York. London.

Griffiths, R.R., Bigelow, G.E., Liebson, I.A., 1986. Human coffee drinking: reinforcing and physical dependence producing effects of caffeine. Journal of Pharmacology and Experimental Therapeutics 239, 416–425.

Griffiths, R.R., Bigelow, G.E., Ator, N.A., 2003. Principles of initial experimental drug abuse liability assessment in humans. Drug and Alcohol Dependence 70, S41–S54.

Grimm, J.W., Hope, B.T., Wise, R.A., Shaham, Y., 2001. Neuroadaptation. Incubation of cocaine craving after withdrawal. Nature 412, 141–142.

Grimm, J.W., Shaham, Y., Hope, B.T., 2002. Effect of cocaine and sucrose withdrawal period on extinction behavior, cue-induced reinstatement, and protein levels of the dopamine transporter and tyrosine hydroxylase in limbic and cortical areas in rats. Behavioural Pharmacology 13, 379–388.

Hall, F.S., Wilkinson, L.S., Humby, T., Inglis, W., Kendall, D.A., Marsden, C.A., Robbins, T.W., 1998. Isolation rearing in rats: pre- and postsynaptic changes in striatal dopaminergic systems. Pharmacology Biochemistry and Behavior 59, 859–872.

Haney, M., Spealman, R., 2008. Controversies in translational research: drug self-administration. Psychopharmacology (Berlin) 199, 403–419.

Haney, M., Maccari, S., Le Moal, M., Simon, H., Piazza, P.V., 1995. Social stress increases the acquisition of cocaine self-administration in male and female rats. Brain Research 698, 46–52.

Haney, M., 2009. Self-administration of cocaine, cannabis and heroin in the human laboratory: benefits and pitfalls. Addiction Biology 14, 9–21.

Harden, K.P., Tucker-Drob, E.M., 2011. Individual differences in the development of sensation seeking and impulsivity during adolescence: further evidence for a dual systems model. Developmental Psychology 47, 739–746.

Hawkins, J.D., Catalano, R.F., Miller, J.Y., 1992. Risk and protective factors for alcohol and other drug problems in adolescence and early adulthood: implications for substance abuse prevention. Psychological Bulletin 112, 64–105.

Hayton, S.J., Mahoney, M.K., Olmstead, M.C., 2012. Behavioral traits predicting alcohol drinking in outbred rats: an investigation of anxiety, novelty seeking, and cognitive flexibility. Alcoholism: Clinical and Experimental Research 36, 594–603.

Heilig, M., Koob, G.F., 2007. A key role for corticotropin-releasing factor in alcohol dependence. Trends in Neurosciences 30, 399–406.

Heilig, M., Koob, G.F., Ekman, R., Britton, K.T., 1994. Corticotropin-releasing factor and neuropeptide Y: role in emotional integration. Trends in Neurosciences 17, 80–85.

Henniger, M.S., Spanagel, R., Wigger, A., Landgraf, R., Holter, S.M., 2002. Alcohol self-administration in two rat lines selectively bred for extremes in anxiety-related behavior. Neuropsychopharmacology 26, 729–736.

Heshmat, S., 2015. Behavioral economics of self-control failure. Yale Journal of Biology and Medicine 88, 333–337.

Heyne, A., Wolffgramm, J., 1998. The development of addiction to d-amphetamine in an animal model: same principles as for alcohol and opiate. Psychopharmacology (Berlin) 140, 510–518.

Heyne, A., 1996. The development of opiate addiction in the rat. Pharmacology Biochemistry and Behavior 53, 11–25.

Higley, J.D., Suomi, S.J., Linnoila, M., 1996a. A nonhuman primate model of type II alcoholism? Part 2. Diminished social competence and excessive aggression correlates with low cerebrospinal fluid 5-

hydroxyindoleacetic acid concentrations. Alcoholism: Clinical and Experimental Research 20, 643−650.

Higley, J.D., Suomi, S.J., Linnoila, M., 1996b. A nonhuman primate model of type II excessive alcohol consumption? Part 1. Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentrations and diminished social competence correlate with excessive alcohol consumption. Alcoholism: Clinical and Experimental Research 20, 629−642.

Hill, S.Y., Powell, B.J., 1976. Cocaine and morphine self-administration: effects of differential rearing. Pharmacology Biochemistry and Behavior 5, 701−704.

Hill, R.T., 1970. Facilitation of conditioned reinforcement as a mechanism of psychomotor stimulation. In: Cost, E., Garattini, S. (Eds.), Amphetamines and Related Compounds. Raven Press, New York, pp. 781−795.

Hogarth, L., Attwood, A.S., Bate, H.A., Munafo, M.R., 2012. Acute alcohol impairs human goal-directed action. Biological Psychology 90, 154−160.

Hokfelt, T., Phillipson, O., Goldstein, M., 1979. Evidence for a dopaminergic pathway in the rat descending from the A11 cell group to the spinal cord. Acta Physiologica Scandinavica 107, 393−395.

Holmes, A., Spanagel, R., Krystal, J.H., 2013. Glutamatergic targets for new alcohol medications. Psychopharmacology 229, 539−554.

Holter, S.M., Spanagel, R., 1999. Effects of opiate antagonist treatment on the alcohol deprivation effect in long-term ethanol-experienced rats. Psychopharmacology (Berlin) 145, 360−369.

Hölter, S.M., Danysz, W., Spanagel, R., 1996. Evidence for alcohol anticraving properties of memantine. European Journal of Pharmacology 314, R1−R2.

Homberg, J.R., van den Akker, M., Raaso, H.S., Wardeh, G., Binnekade, R., Schoffelmeer, A.N., de Vries, T.J., 2002. Enhanced motivation to self-administer cocaine is predicted by self-grooming behaviour and relates to dopamine release in the rat medial prefrontal cortex and amygdala. European Journal of Neuroscience 15, 1542−1550.

Hudson, A., Stamp, J.A., 2011. Ovarian hormones and propensity to drug relapse: a review. Neuroscience and Biobehavioral Reviews 35, 427−436.

Hyman, S.E., Malenka, R.C., Nestler, E.J., 2006. Neural mechanisms of addiction: the role of reward-related learning and memory. Annual Review of Neuroscience 29, 565−598.

Jacobs, E.A., Bickel, W.K., 1999. Modeling drug consumption in the clinic using simulation procedures: demand for heroin and cigarettes in opioid-dependent outpatients. Experimental and Clinical Psychopharmacology 7, 412−426.

Justinova, Z., Goldberg, S.R., Heishman, S.J., Tanda, G., 2005. Self-administration of cannabinoids by experimental animals and human marijuana smokers. Pharmacology Biochemistry and Behavior 81, 285−299.

Kabbaj, M., Norton, C.S., Kollack-Walker, S., Watson, S.J., Robinson, T.E., Akil, H., 2001. Social defeat alters the acquisition of cocaine self-administration in rats: role of individual differences in cocaine-taking behavior. Psychopharmacology (Berlin) 158, 382−387.

Kalivas, P.W., Nakamura, M., 1999. Neural systems for behavioral activation and reward. Current Opinion in Neurobiology 9, 223−227.

Kalivas, P.W., Volkow, N.D., 2005. The neural basis of addiction: a pathology of motivation and choice. American Journal of Psychiatry 162, 1403−1413.

Kalivas, P.W., 2005. How do we determine which drug-induced neuroplastic changes are important? Nature Neuroscience 8, 1440−1441.

Katner, S.N., Magalong, J.G., Weiss, F., 1999. Reinstatement of alcohol-seeking behavior by drug-associated discriminative stimuli after prolonged extinction in the rat. Neuropsychopharmacology 20, 471−479.

Katz, J.L., Higgins, S.T., 2003. The validity of the reinstatement model of craving and relapse to drug use. Psychopharmacology (Berlin) 168, 21−30.

Kelleher, R.T., Morse, W.H., 1968. Determinants of the specificity of behavioral effects of drugs. Ergebnisse der Physiologie 60, 1−56.

Kelley, A.E., 2004. Ventral striatal control of appetitive motivation: role in ingestive behavior and reward-related learning. Neuroscience and Biobehavioral Reviews 27, 765−776.

Kelly, T.H., Robbins, G., Martin, C.A., Fillmore, M.T., Lane, S.D., Harrington, N.G., Rush, C.R., 2006. Individual differences in drug abuse vulnerability: d-amphetamine and sensation-seeking status. Psychopharmacology (Berlin) 189, 17−25.

Khantzian, E.J., 1985. The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. American Journal of Psychiatry 142, 1259−1264.

Kirby, K.N., Petry, N.M., 2004. Heroin and cocaine abusers have higher discount rates for delayed rewards than alcoholics or non-drug-using controls. Addiction 99, 461−471.

Klebaur, J.E., Bardo, M.T., 1999. Individual differences in novelty seeking on the playground maze predict amphetamine conditioned place preference. Pharmacology Biochemistry and Behavior 63, 131−136.

Koob, G.F., Le Moal, M., 1997. Drug abuse: hedonic homeostatic dysregulation. Science 278, 52−58.

Koob, G.F., Le Moal, M., 2001. Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology 24, 97−129.

Koob, G.F, Le Moal, M., 2005. Neurobiology of Addiction, first ed. Elsevier Science.

Koob, G.F., Volkow, N.D., 2010. Neurocircuitry of addiction. Neuropsychopharmacology 35, 217−238.

Koob, G.F., 2009. Neurobiological substrates for the dark side of compulsivity in addiction. Neuropharmacology 56 (Suppl. 1), 18−31.

Kosten, T.A., Gawin, F.H., Kosten, T.R., Rounsaville, B.J., 1993. Gender differences in cocaine use and treatment response. Journal of Substance Abuse Treatment 10, 63−66.

Krystal, J.H., Petrakis, I.L., Mason, G., Trevisan, L., D'Souza, D.C., 2003. *N*-methyl-*D*-aspartate glutamate receptors and alcoholism: reward, dependence, treatment, and vulnerability. Pharmacology and Therapeutics 99, 79−94.

Kudryavtseva, N.N., Madorskaya, I.A., Bakshtanovskaya, I.V., 1991. Social success and voluntary ethanol consumption in mice of C57BL/6J and CBA/Lac strains. Physiology and Behavior 50, 143−146.

Kudryavtseva, N., Gerrits, M.A., Avgustinovich, D.F., Tenditnik, M.V., Van Ree, J.M., 2006. Anxiety and ethanol consumption in victorious and defeated mice; effect of kappa-opioid receptor activation. European Neuropsychopharmacology 16, 504−511.

Kushner, M.G., Wall, M.M., Krueger, R.F., Sher, K.J., Maurer, E., Thuras, P., Lee, S., 2012. Alcohol dependence is related to overall internalizing psychopathology load rather than to particular internalizing disorders: evidence from a national sample. Alcoholism: Clinical and Experimental Research 36, 325−331.

Kutschera, W., Rom, W., 2000. Ötzi, the prehistoric Iceman. Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms 164−165, 12−22.

Langleben, D.D., Ruparel, K., Elman, I., Busch-Winokur, S., Pratiwadi, R., Loughead, J., O'Brien, C.P., Childress, A.R., 2008. Acute effect of methadone maintenance dose on brain FMRI response to heroin-related cues. American Journal of Psychiatry 165, 390–394.

Lesscher, H.M., Spoelder, M., Rotte, M.D., Janssen, M.J., Hesseling, P., Lozeman-van't Klooster, J.G., Baars, A.M., Vanderschuren, L.J., 2015. Early social isolation augments alcohol consumption in rats. Behavioural Pharmacology 26, 673–680.

Levesque, D., Gagnon, S., Di Paolo, T., 1989. Striatal D1 dopamine receptor density fluctuates during the rat estrous cycle. Neuroscience Letters 98, 345–350.

Leyton, M., Boileau, I., Benkelfat, C., Diksic, M., Baker, G., Dagher, A., 2002. Amphetamine-induced increases in extracellular dopamine, drug wanting, and novelty seeking: a PET/[^{11}C]raclopride study in healthy men. Neuropsychopharmacology 27, 1027–1035.

Lin, J.Y., Arthurs, J., Reilly, S., 2014. Conditioned taste aversion, drugs of abuse and palatability. Neuroscience and Biobehavioral Reviews 45, 28–45.

Linsenbardt, D.N., Boehm, S.L., 2014. Alterations in the rate of binge ethanol consumption: implications for preclinical studies in mice. Addiction Biology 19, 812–825.

Liu, X., Matochik, J.A., Cadet, J.L., London, E.D., 1998. Smaller volume of prefrontal lobe in polysubstance abusers: a magnetic resonance imaging study. Neuropsychopharmacology 18, 243–252.

Madden, G.J., Bickel, W.K., 1999. Abstinence and price effects on demand for cigarettes: a behavioral-economic analysis. Addiction 94, 577–588.

Mantsch, J.R., Katz, E.S., 2007. Elevation of glucocorticoids is necessary but not sufficient for the escalation of cocaine self-administration by chronic electric footshock stress in rats. Neuropsychopharmacology 32, 367–376.

Manzo, L., Gomez, M.J., Callejas-Aguilera, J.E., Donaire, R., Sabariego, M., Fernandez-Teruel, A., Canete, A., Blazquez, G., Papini, M.R., Torres, C., 2014. Relationship between ethanol preference and sensation/novelty seeking. Physiology and Behavior 133, 53–60.

Marchant, N.J., Rabei, R., Kaganovsky, K., Caprioli, D., Bossert, J.M., Bonci, A., Shaham, Y., 2014. A critical role of lateral hypothalamus in context-induced relapse to alcohol seeking after punishment-imposed abstinence. Journal of Neuroscience 34, 7447–7457.

Marhe, R., Luijten, M., Franken, I.H., 2014. The clinical relevance of neurocognitive measures in addiction. Frontiers in Psychiatry 4, 185.

Marquenie, L.A., Schade, A., van Balkom, A.J., Comijs, H.C., de Graaf, R., Vollebergh, W., van Dyck, R., van den Brink, W., 2007. Origin of the comorbidity of anxiety disorders and alcohol dependence: findings of a general population study. European Addiction Research 13, 39–49.

Martinez, D., Broft, A., Foltin, R.W., Slifstein, M., Hwang, D.R., Huang, Y., Perez, A., Frankle, W.G., Cooper, T., Kleber, H.D., Fischman, M.W., Laruelle, M., 2004. Cocaine dependence and d2 receptor availability in the functional subdivisions of the striatum: relationship with cocaine-seeking behavior. Neuropsychopharmacology 29, 1190–1202.

Martinez, D., Gil, R., Slifstein, M., Hwang, D.R., Huang, Y., Perez, A., Kegeles, L., Talbot, P., Evans, S., Krystal, J., Laruelle, M., Abi-Dargham, A., 2005. Alcohol dependence is associated with blunted dopamine transmission in the ventral striatum. Biological Psychiatry 58, 779–786.

Marusich, J.A., Bardo, M.T., 2009. Differences in impulsivity on a delay-discounting task predict self-administration of a low unit dose of methylphenidate in rats. Behavioural Pharmacology 20, 447–454.

Mayfield, R.D., Harris, R.A., Schuckit, M.A., 2008. Genetic factors influencing alcohol dependence. British Journal of Pharmacology 154, 275–287.

McClernon, F.J., Kozink, R.V., Lutz, A.M., Rose, J.E., 2009. 24-h smoking abstinence potentiates fMRI-BOLD activation to smoking cues in cerebral cortex and dorsal striatum. Psychopharmacology (Berlin) 204, 25–35.

McKay, J.R., Rutherford, M.J., Alterman, A.I., Cacciola, J.S., 1996. Development of the cocaine relapse interview: an initial report. Addiction 91, 535–548.

McKinney, W.T., 1998. Models of Mental Disorders: A New Comparative Psychiatry. Springer, US.

McNamara, R., Dalley, J.W., Robbins, T.W., Everitt, B.J., Belin, D., 2010. Trait-like impulsivity does not predict escalation of heroin self-administration in the rat. Psychopharmacology (Berlin) 212, 453–464.

Mehlman, P.T., Higley, J.D., Faucher, I., Lilly, A.A., Taub, D.M., Vickers, J., Suomi, S.J., Linnoila, M., 1994. Low CSF 5-HIAA concentrations and severe aggression and impaired impulse control in nonhuman primates. American Journal of Psychiatry 151, 1485–1491.

Merikangas, K.R., McClair, V.L., 2012. Epidemiology of substance use disorders. Human Genetics 131, 779–789.

Merikangas, K.R., Metha, R.L., Molnar, B.E., Walters, E.E., Swendsen, J.D., Aguilar-Gaziola, S., Bijl, R., Borges, G., Caraveo-Anduaga, J.J., DeWit, D.J., Kolody, B., Vega, W.A., Wittchen, H.U., Kessler, R.C., 1998. Comorbidity of substance use disorders with mood and anxiety disorders: results of the International Consortium in Psychiatric Epidemiology. Addictive Behaviors 23, 893–907.

Miczek, K.A., Mutschler, N.H., 1996. Activational effects of social stress on IV cocaine self-administration in rats. Psychopharmacology (Berlin) 128, 256–264.

Mitchell, M.R., Potenza, M.N., 2014. Recent insights into the neurobiology of impulsivity. Current Addiction Reports 1, 309–319.

Mitchell, M.R., Weiss, V.G., Beas, B.S., Morgan, D., Bizon, J.L., Setlow, B., 2014. Adolescent risk taking, cocaine self-administration, and striatal dopamine signaling. Neuropsychopharmacology 39, 955–962.

Modell, J.G., Glaser, F.B., Cyr, L., Mountz, J.M., 1992. Obsessive and compulsive characteristics of craving for alcohol in alcohol abuse and dependence. Alcoholism: Clinical and Experimental Research 16, 272–274.

Molander, A., Vengeliene, V., Heilig, M., Wurst, W., Deussing, J.M., Spanagel, R., 2012. Brain-specific inactivation of the Crhr1 gene inhibits post-dependent and stress-induced alcohol intake, but does not affect relapse-like drinking. Neuropsychopharmacology 37, 1047–1056.

Montanari, C., Stendardo, E., De Luca, M.T., Meringolo, M., Contu, L., Badiani, A., 2015. Differential vulnerability to relapse into heroin versus cocaine-seeking as a function of setting. Psychopharmacology (Berlin) 232, 2415–2424.

Monterosso, J., Piray, P., Luo, S., 2012. Neuroeconomics and the study of addiction. Biological Psychiatry 72, 107–112.

Morgan, D., Grant, K.A., Gage, H.D., Mach, R.H., Kaplan, J.R., Prioleau, O., Nader, S.H., Buchheimer, N., Ehrenkaufer, R.L., Nader, M.A., 2002. Social dominance in monkeys: dopamine D2 receptors and cocaine self-administration. Nature Neuroscience 5, 169–174.

Morse, A.C., Erwin, V.G., Jones, B.C., 1993. Strain and housing affect cocaine self-selection and open-field locomotor activity in mice. Pharmacology Biochemistry and Behavior 45, 905–912.

Nadal, R., Armario, A., Janak, P.H., 2002. Positive relationship between activity in a novel environment and operant ethanol self-administration in rats. Psychopharmacology (Berlin) 162, 333–338.

Nader, M.A., Czoty, P.W., Nader, S.H., Morgan, D., 2012. Nonhuman primate models of social behavior and cocaine abuse. Psychopharmacology (Berlin) 224, 57–67.

Neisewander, J.L., Baker, D.A., Fuchs, R.A., Tran-Nguyen, L.T., Palmer, A., Marshall, J.F., 2000. Fos protein expression and cocaine-seeking behavior in rats after exposure to a cocaine self-administration environment. Journal of Neuroscience 20, 798–805.

Neisewander, J.L., Peartree, N.A., Pentkowski, N.S., 2012. Emotional valence and context of social influences on drug abuse-related behavior in animal models of social stress and prosocial interaction. Psychopharmacology (Berlin) 224, 33–56.

Nestler, E.J., Aghajanian, G.K., 1997. Molecular and cellular basis of addiction. Science 278, 58–63.

Newlin, D.B., Thomson, J.B., 1990. Alcohol challenge with sons of alcoholics: a critical review and analysis. Psychological Bulletin 108, 383–402.

Nutt, D.J., Lingford-Hughes, A., Erritzoe, D., Stokes, P.R., 2015. The dopamine theory of addiction: 40 years of highs and lows. Nature Reviews Neuroscience 16, 305–312.

O'Brien, C.P., Volkow, N., Li, T.K., 2006. What's in a word? Addiction versus dependence in DSM-V. American Journal of Psychiatry 163, 764–765.

O'Brien, J.M., 1980. Alexander and Dionysus: the invisible enemy. Annals of Scholarship 1, 83–105.

Olds, J., Milner, P., 1954. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. Journal of Comparative and Physiological Psychology 47, 419–427.

O'Leary, T.A., Rohsenow, D.J., Martin, R., Colby, S.M., Eaton, C.A., Monti, P.M., 2000. The relationship between anxiety levels and outcome of cocaine abuse treatment. American Journal of Drug and Alcohol Abuse 26, 179–194.

Olive, M.F., 2009. Metabotropic glutamate receptor ligands as potential therapeutics for addiction. Current Drug Abuse Reviews 2, 83–98.

Panlilio, L.V., Goldberg, S.R., 2007. Self-administration of drugs in animals and humans as a model and an investigative tool. Addiction 102, 1863–1870.

Parker, L.A., 2003. Taste avoidance and taste aversion: evidence for two different processes. Learning and Behavior 31, 165–172.

Parrott, A.C., 2004. MDMA (3,4-Methylenedioxymethamphetamine) or ecstasy: the neuropsychobiological implications of taking it at dances and raves. Neuropsychobiology 50, 329–335.

Parsegian, A., Glen Jr., W.B., Lavin, A., See, R.E., 2011. Methamphetamine self-administration produces attentional set-shifting deficits and alters prefrontal cortical neurophysiology in rats. Biological Psychiatry 69, 253–259.

Paus, T., 2005. Mapping brain maturation and cognitive development during adolescence. Trends in Cognitive Sciences 9, 60–68.

Pearson, M., Sweeting, H., West, P., Young, R., Gordon, J., Turner, K., 2006. Adolescent substance use in different social and peer contexts: a social network analysis. Drugs: Education, Prevention and Policy 13, 519–536.

Pelloux, Y., Costentin, J., Duterte-Boucher, D., 2004. Differential effects of novelty exposure on place preference conditioning to amphetamine and its oral consumption. Psychopharmacology (Berlin) 171, 277–285.

Pelloux, Y., Costentin, J., Duterte-Boucher, D., 2006. Novelty preference predicts place preference conditioning to morphine and its oral consumption in rats. Pharmacology Biochemistry and Behavior 84, 43–50.

Pelloux, Y., Costentin, J., Duterte-Boucher, D., 2009. Anxiety increases the place conditioning induced by cocaine in rats. Behavioural Brain Research 197, 311–316.

Pelloux, Y., Costentin, J., Duterte-Boucher, D., 2015. Differential involvement of anxiety and novelty preference levels on oral ethanol consumption in rats. Psychopharmacology (Berlin) 232, 2711–2721.

Perkins, K.A., Epstein, L.H., Grobe, J., Fonte, C., 1994. Tobacco abstinence, smoking cues, and the reinforcing value of smoking. Pharmacology Biochemistry and Behavior 47, 107–112.

Perkins, K.A., Grobe, J.E., Weiss, D., Fonte, C., Caggiula, A., 1996. Nicotine preference in smokers as a function of smoking abstinence. Pharmacology Biochemistry and Behavior 55, 257–263.

Perry, J.L., Larson, E.B., German, J.P., Madden, G.J., Carroll, M.E., 2005. Impulsivity (delay discounting) as a predictor of acquisition of IV cocaine self-administration in female rats. Psychopharmacology (Berlin) 178, 193–201.

Peters, S., Slattery, D.A., Flor, P.J., Neumann, I.D., Reber, S.O., 2013. Differential effects of baclofen and oxytocin on the increased ethanol consumption following chronic psychosocial stress in mice. Addiction Biology 18, 66–77.

Phillips, G.D., Howes, S.R., Whitelaw, R.B., Robbins, T.W., Everitt, B.J., 1994a. Isolation rearing impairs the reinforcing efficacy of intravenous cocaine or intra-accumbens d-amphetamine: impaired response to intra-accumbens D1 and D2/D3 dopamine receptor antagonists. Psychopharmacology (Berlin) 115, 419–429.

Phillips, G.D., Howes, S.R., Whitelaw, R.B., Wilkinson, L.S., Robbins, T.W., Everitt, B.J., 1994b. Isolation rearing enhances the locomotor response to cocaine and a novel environment, but impairs the intravenous self-administration of cocaine. Psychopharmacology (Berlin) 115, 407–418.

Piazza, P.V., Deminiere, J.M., Le Moal, M., Simon, H., 1989. Factors that predict individual vulnerability to amphetamine self-administration. Science 245, 1511–1513.

Piazza, P.V., Deminiere, J.M., Le Moal, M., Simon, H., 1990. Stress- and pharmacologically-induced behavioral sensitization increases vulnerability to acquisition of amphetamine self-administration. Brain Research 514, 22–26.

Piazza, P.V., Deroche-Gamonent, V., Rouge-Pont, F., Le Moal, M., 2000. Vertical shifts in self-administration dose-response functions predict a drug-vulnerable phenotype predisposed to addiction. Journal of Neuroscience 20, 4226–4232.

Pildaín, L.V., Vengeliene, V., Matthäus, F., 2013. New measurement criteria for studying alcohol drinking and relapse in rodents. In Silico Pharmacology 1, 1–10.

Pohorecky, L.A., 2006. Housing and rank status of male Long-Evans rats modify ethanol's effect on open-field behaviors. Psychopharmacology (Berlin) 185, 289–297.

Pohorecky, L.A., 2008. Psychosocial stress and chronic ethanol ingestion in male rats: effects on elevated plus maze behavior and ultrasonic vocalizations. Physiology and Behavior 94, 432–447.

Pohorecky, L.A., 2010. Acute novel stressors modify ethanol intake of psychosocially stressed rats. Pharmacology Biochemistry and Behavior 95, 390–400.

Porter, J.N., Olsen, A.S., Gurnsey, K., Dugan, B.P., Jedema, H.P., Bradberry, C.W., 2011. Chronic cocaine self-administration in rhesus monkeys: impact on associative learning, cognitive control, and working memory. Journal of Neuroscience 31, 4926–4934.

Potenza, M.N., Hong, K.I., Lacadie, C.M., Fulbright, R.K., Tuit, K.L., Sinha, R., 2012. Neural correlates of stress-induced and cue-induced drug craving: influences of sex and cocaine dependence. American Journal of Psychiatry 169, 406–414.

Poulos, C.X., Cappell, H., 1991. Homeostatic theory of drug tolerance: a general model of physiological adaptation. Psychological Review 98, 390–408.

Poulos, C.X., Le, A.D., Parker, J.L., 1995. Impulsivity predicts individual susceptibility to high levels of alcohol self-administration. Behavioural Pharmacology 6, 810–814.

Radwanska, K., Kaczmarek, L., 2012. Characterization of an alcohol addiction-prone phenotype in mice. Addiction Biology 17, 601–612.

Ramsey, N.F., Van Ree, J.M., 1993. Emotional but not physical stress enhances intravenous cocaine self-administration in drug-naive rats. Brain Research 608, 216–222.

Reddy, T.E., Pauli, F., Sprouse, R.O., Neff, N.F., Newberry, K.M., Garabedian, M.J., Myers, R.M., 2009. Genomic determination of the glucocorticoid response reveals unexpected mechanisms of gene regulation. Genome Research 19, 2163–2171.

Richards, J.M., Plate, R.C., Ernst, M., 2013. A systematic review of fMRI reward paradigms used in studies of adolescents vs. adults: the impact of task design and implications for understanding neurodevelopment. Neuroscience and Biobehavioral Reviews 37, 976–991.

Rietschel, M., Treutlein, J., 2013. The genetics of alcohol dependence. Annals of the New York Academy of Sciences 1282, 39–70.

Roache, J.D., Griffiths, R.R., 1985. Comparison of triazolam and pentobarbital: performance impairment, subjective effects and abuse liability. Journal of Pharmacology and Experimental Therapeutics 234, 120–133.

Robbins, T.W., 1976. Relationship between reward-enhancing and stereotypical effects of psychomotor stimulant drugs. Nature 264, 57–59.

Roberts, D.C., Loh, E.A., Vickers, G., 1989. Self-administration of cocaine on a progressive ratio schedule in rats: dose-response relationship and effect of haloperidol pretreatment. Psychopharmacology (Berlin) 97, 535–538.

Robinet, P.M., Rowlett, J.K., Bardo, M.T., 1998. Individual differences in novelty-induced activity and the rewarding effects of novelty and amphetamine in rats. Behavioural Processes 44, 1–9.

Robinson, T.E., Berridge, K.C., 1993. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Research. Brain Research Reviews 18, 247–291.

Robinson, T.E., Berridge, K.C., 2000. The psychology and neurobiology of addiction: an incentive-sensitization view. Addiction 95 (Suppl. 2), S91–S117.

Robinson, T.E., Berridge, K.C., 2003. Addiction. Annual Review of Psychology 54, 25–53.

Rosenwasser, A.M., Fixaris, M.C., Crabbe, J.C., Brooks, P.C., Ascheid, S., 2013. Escalation of intake under intermittent ethanol access in diverse mouse genotypes. Addiction Biology 18, 496–507.

Rounsaville, B.J., Anton, S.F., Carroll, K., Budde, D., Prusoff, B.A., Gawin, F., 1991. Psychiatric diagnoses of treatment-seeking cocaine abusers. Archives of General Psychiatry 48, 43–51.

Rusby, J.C., Forrester, K.K., Biglan, A., Metzler, C.W., 2005. Relationships between peer harassment and adolescent problem behaviors. Journal of Early Adolescence 25, 453–477.

Russo, E.B., Jiang, H.E., Li, X., Sutton, A., Carboni, A., del Bianco, F., Mandolino, G., Potter, D.J., Zhao, Y.X., Bera, S., Zhang, Y.B., Lu, E.G., Ferguson, D.K., Hueber, F., Zhao, L.C., Liu, C.J., Wang, Y.F., Li, C.S., 2008. Phytochemical and genetic analyses of ancient cannabis from Central Asia. Journal of Experimental Botany 59, 4171–4182.

Rusted, J.M., Mackee, A., Williams, R., Willner, P., 1998. Deprivation state but not nicotine content of the cigarette affects responding by smokers on a progressive ratio task. Psychopharmacology (Berlin) 140, 411–417.

Safari Hajat Aghaii, S., Kamaly, A., Esfahani, M., 2012. Meta-analysis of individual and environmental factors that influence People's addiction tendencies. International Journal of High Risk Behaviors and Addiction 1, 92–99.

Salimov, R.M., Salimova, N.B., 1993. The alcohol deprivation effect in hybrid mice. Drug and Alcohol Dependence 187–191.

Sanchez, V., Moore, C.F., Brunzell, D.H., Lynch, W.J., 2013. Effect of wheel-running during abstinence on subsequent nicotine-seeking in rats. Psychopharmacology (Berlin) 227, 403–411.

Sanchis-Segura, C., Spanagel, R., 2006. Behavioural assessment of drug reinforcement and addictive features in rodents: an overview. Addiction Biology 11, 2–38.

Sanchis-Segura, C., Cline, B.H., Marsicano, G., Lutz, B., Spanagel, R., 2004. Reduced sensitivity to reward in CB1 knockout mice. Psychopharmacology (Berlin) 176, 223–232.

Sanchis-Segura, C., Borchardt, T., Vengeliene, V., Zghoul, T., Bachteler, D., Gass, P., Sprengel, R., Spanagel, R., 2006. Involvement of the AMPA receptor GluR-C subunit in alcohol-seeking behavior and relapse. Journal of Neuroscience 26, 1231–1238.

Sarkar, D.K., 2012. Circadian genes, the stress axis, and alcoholism. Alcohol Research 34, 362–366.

Sartor, C.E., Lynskey, M.T., Heath, A.C., Jacob, T., True, W., 2007. The role of childhood risk factors in initiation of alcohol use and progression to alcohol dependence. Addiction 102, 216–225.

Schank, J.R., Ryabinin, A.E., Giardino, W.J., Ciccocioppo, R., Heilig, M., 2012. Stress-related neuropeptides and addictive behaviors: beyond the usual suspects. Neuron 76, 192–208.

Schenk, S., Lacelle, G., Gorman, K., Amit, Z., 1987. Cocaine self-administration in rats influenced by environmental conditions: implications for the etiology of drug abuse. Neuroscience Letters 81, 227–231.

Schenk, S., Robinson, B., Amit, Z., 1988. Housing conditions fail to affect the intravenous self-administration of amphetamine. Pharmacology Biochemistry and Behavior 31, 59–62.

Schenk, S., Harper, D.N., Do, J., 2011. Novel object recognition memory: measurement issues and effects of MDMA self-administration following short inter-trial intervals. Journal of Psychopharmacology 25, 1043–1052.

Schifano, F., 2000. Potential human neurotoxicity of MDMA ('Ecstasy'): subjective self-reports, evidence from an Italian drug addiction centre and clinical case studies. Neuropsychobiology 42, 25–33.

Schippers, M.C., Binnekade, R., Schoffelmeer, A.N., Pattij, T., De Vries, T.J., 2012. Unidirectional relationship between heroin self-administration and impulsive decision-making in rats. Psychopharmacology (Berlin) 219, 443–452.

Schneider Jr., R., Ottoni, G.L., de Carvalho, H.W., Elisabetsky, E., Lara, D.R., 2015. Temperament and character traits associated with the use of alcohol, cannabis, cocaine, benzodiazepines, and

hallucinogens: evidence from a large Brazilian web survey. Revista Brasileria de Psiquiatria 37, 31–39.

Schultz, W., 2000. Multiple reward signals in the brain. Nature Reviews Neuroscience 1, 199–207.

Selemon, L.D., 2014. Frontal lobe synaptic plasticity in development and disease: modulation by the dopamine d1 receptor. Current Pharmaceutical Design 20, 5194–5201.

Shaham, Y., Stewart, J., 1994. Exposure to mild stress enhances the reinforcing efficacy of intravenous heroin self-administration in rats. Psychopharmacology (Berlin) 114, 523–527.

Shaham, Y., Shalev, U., Lu, L., De Wit, H., Stewart, J., 2003. The reinstatement model of drug relapse: history, methodology and major findings. Psychopharmacology (Berlin) 168, 3–20.

Shaham, Y., 1993. Immobilization stress-induced oral opioid self-administration and withdrawal in rats: role of conditioning factors and the effect of stress on "relapse" to opioid drugs. Psychopharmacology (Berlin) 111, 477–485.

Shalev, U., Morales, M., Hope, B., Yap, J., Shaham, Y., 2001. Time-dependent changes in extinction behavior and stress-induced reinstatement of drug seeking following withdrawal from heroin in rats. Psychopharmacology (Berlin) 156, 98–107.

Sheldrake, R., McKenna, T.K., Abraham, R., 1998. The Evolutionary Mind: Conversations on Science, Imagination & Spirit. Monkfish Book Publishing Company.

Shepard, J.D., Bossert, J.M., Liu, S.Y., Shaham, Y., 2004. The anxiogenic drug yohimbine reinstates methamphetamine seeking in a rat model of drug relapse. Biological Psychiatry 55, 1082–1089.

Sher, K.J., 1985. Subjective effects of alcohol: the influence of setting and individual differences in alcohol expectancies. Journal of Studies on Alcohol and Drugs 46, 137–146.

Sillaber, I., Rammes, G., Zimmermann, S., Mahal, B., Zieglgansberger, W., Wurst, W., Holsboer, F., Spanagel, R., 2002. Enhanced and delayed stress-induced alcohol drinking in mice lacking functional CRH1 receptors. Science 296, 931–933.

Sinclair, J.D., Senter, R.J., 1967. Increased preference for ethanol in rats following alcohol deprivation. Psychonomic Science 8, 11–12.

Sinclair, J.D., 1971. The alcohol-deprivation effect in monkeys. Psychonomic Science 25, 21–22.

Sinha, R., 2009. Stress and addiction: a dynamic interplay of genes, environment, and drug intake. Biological Psychiatry 66, 100–101.

Smith, W., 1898. Dictionary of Greek and Roman Antiquities. John Murray, London.

Sofuoglu, M., Mitchell, E., Kosten, T.R., 2004. Effects of progesterone treatment on cocaine responses in male and female cocaine users. Pharmacology Biochemistry and Behavior 78, 699–705.

Solomon, R.L., Corbit, J.D., 1974. An opponent-process theory of motivation. I. Temporal dynamics of affect. Psychological Review 81, 119–145.

Somerville, L.H., Jones, R.M., Casey, B.J., 2010. A time of change: behavioral and neural correlates of adolescent sensitivity to appetitive and aversive environmental cues. Brain and Cognition 72, 124–133.

Sonntag, K.C., Brenhouse, H.C., Freund, N., Thompson, B.S., Puhl, M., Andersen, S.L., 2014. Viral over-expression of D1 dopamine receptors in the prefrontal cortex increase high-risk behaviors in adults: comparison with adolescents. Psychopharmacology (Berlin) 231, 1615–1626.

Spanagel, R., Heilig, M., 2005. Addiction and its brain science. Addiction 100, 1813–1822.

Spanagel, R., Holter, S.M., 1999. Long-term alcohol self-administration with repeated alcohol deprivation phases: an animal model of alcoholism? Alcohol and Alcoholism 34, 231–243.

Spanagel, R., Vengeliene, V., 2013. New pharmacological treatment strategies for relapse prevention. Current Topics in Behavioral Neurosciences 13, 583–609.

Spanagel, R., Montkowski, A., Allingham, K., Stohr, T., Shoaib, M., Holsboer, F., Landgraf, R., 1995. Anxiety: a potential predictor of vulnerability to the initiation of ethanol self-administration in rats. Psychopharmacology (Berlin) 122, 369–373.

Spanagel, R., Pendyala, G., Abarca, C., Zghoul, T., Sanchis-Segura, C., Magnone, M.C., Lascorz, J., Depner, M., Holzberg, D., Soyka, M., Schreiber, S., Matsuda, F., Lathrop, M., Schumann, G., Albrecht, U., 2005. The clock gene Per2 influences the glutamatergic system and modulates alcohol consumption. Nature Medicine 11, 35–42.

Spanagel, R., Noori, H.R., Heilig, M., 2014a. Stress and alcohol interactions: animal studies and clinical significance. Trends in Neuroscience 37, 219–227.

Spanagel, R., Vengeliene, V., Jandeleit, B., Fischer, W.N., Grindstaff, K., Zhang, X., Gallop, M.A., Krstew, E.V., Lawrence, A.J., Kiefer, F., 2014b. Acamprosate produces its anti-relapse effects via calcium. Neuropsychopharmacology 39, 783–791.

Spanagel, R., 2003. The role of the glutamatergic system in alcohol addiction. Fortschritte der Neurologie Psychiatrie 71 (Suppl. 1), S33–S35.

Spanagel, R., 2009. Alcoholism: a systems approach from molecular physiology to addictive behavior. Physiological Reviews 89, 649–705.

Squire, L.R., Kandel, E.R., 2009. Memory: From Mind to Molecules. Roberts & Company.

Stein, J.S., Johnson, P.S., Renda, C.R., Smits, R.R., Liston, K.J., Shahan, T.A., Madden, G.J., 2013. Early and prolonged exposure to reward delay: effects on impulsive choice and alcohol self-administration in male rats. Experimental and Clinical Psychopharmacology 21, 172–180.

Stephens, D.N., Duka, T., Crombag, H.S., Cunningham, C.L., Heilig, M., Crabbe, J.C., 2010. Reward sensitivity: issues of measurement, and achieving consilience between human and animal phenotypes. Addiction Biology 15, 145–168.

Stewart, J., de Wit, H., Eikelboom, R., 1984. Role of unconditioned and conditioned drug effects in the self-administration of opiates and stimulants. Psychological Review 91, 251–268.

Stuber, G.D., Sparta, D.R., Stamatakis, A.M., van Leeuwen, W.A., Hardjoprajitno, J.E., Cho, S., Tye, K.M., Kempadoo, K.A., Zhang, F., Deisseroth, K., Bonci, A., 2011. Excitatory transmission from the amygdala to nucleus accumbens facilitates reward seeking. Nature 475, 377–380.

Sutker, P.B., Archer, R.P., Allain, A.N., 1978. Drug abuse patterns, personality characteristics, and relationships with sex, race, and sensation seeking. Journal of Consulting and Clinical Psychology 46, 1374–1378.

Tetrault, J.M., Desai, R.A., Becker, W.C., Fiellin, D.A., Concato, J., Sullivan, L.E., 2008. Gender and non-medical use of prescription opioids: results from a national US survey. Addiction 103, 258–268.

Thanos, P.K., Tucci, A., Stamos, J., Robison, L., Wang, G.J., Anderson, B.J., Volkow, N.D., 2010. Chronic forced exercise during adolescence decreases cocaine conditioned place preference in Lewis rats. Behavioural Brain Research 215, 77–82.

Thiel, K.J., Okun, A.C., Neisewander, J.L., 2008. Social reward-conditioned place preference: a model revealing an interaction between cocaine and social context rewards in rats. Drug and Alcohol Dependence 96, 202–212.

Thiel, K.J., Sanabria, F., Neisewander, J.L., 2009. Synergistic interaction between nicotine and social rewards in adolescent male rats. Psychopharmacology (Berlin) 204, 391–402.

Tidey, J.W., Miczek, K.A., 1997. Acquisition of cocaine self-administration after social stress: role of accumbens dopamine. Psychopharmacology (Berlin) 130, 203–212.

Tiffany, S.T., 1990. A cognitive model of drug urges and drug-use behavior: role of automatic and nonautomatic processes. Psychological Review 97, 147–168.

Timpl, P., Spanagel, R., Sillaber, I., Kresse, A., Reul, J.M., Stalla, G.K., Blanquet, V., Steckler, T., Holsboer, F., Wurst, W., 1998. Impaired stress response and reduced anxiety in mice lacking a functional corticotropin-releasing hormone receptor 1. Nature Genetics 19, 162–166.

Todd, T.P., Winterbauer, N.E., Bouton, M.E., 2012. Contextual control of appetite. Renewal of inhibited food-seeking behavior in sated rats after extinction. Appetite 58, 484–489.

Tsai, G., Gastfriend, D.R., Coyle, J.T., 1995. The glutamatergic basis of human alcoholism. American Journal of Psychiatry 152, 332.

Tzschentke, T.M., 2007. Measuring reward with the conditioned place preference (CPP) paradigm: update of the last decade. Addiction Biology 12, 227–462.

Van Etten, M.L., Anthony, J.C., 2001. Male-female differences in transitions from first drug opportunity to first use: searching for subgroup variation by age, race, region, and urban status. Journal of Women's Health and Gender-Based Medicine 10, 797–804.

Vanderschuren, L.J., Ahmed, S.H., 2013. Animal studies of addictive behavior. Cold Spring Harbor Perspectives in Medicine 3, a011932.

Vanderschuren, L.J., Everitt, B.J., 2004. Drug seeking becomes compulsive after prolonged cocaine self-administration. Science 305, 1017–1019.

Vengeliene, V., Bachteler, D., Danysz, W., Spanagel, R., 2005. The role of the NMDA receptor in alcohol relapse: a pharmacological mapping study using the alcohol deprivation effect. Neuropharmacology 48, 822–829.

Vengeliene, V., Bilbao, A., Molander, A., Spanagel, R., 2008. Neuropharmacology of alcohol addiction. British Journal of Pharmacology 154, 299–315.

Vengeliene, V., Bilbao, A., Spanagel, R., 2014. The alcohol deprivation effect model for studying relapse behavior: a comparison between rats and mice. Alcohol 48, 313–320.

Ventura, R., Morrone, C., Puglisi-Allegra, S., 2007. Prefrontal/accumbal catecholamine system determines motivational salience attribution to both reward- and aversion-related stimuli. Proceedings of the National Academy of Sciences of the United States of America 104, 5181–5186.

Vidal-Infer, A., Arenas, M.C., Daza-Losada, M., Aguilar, M.A., Minarro, J., Rodriguez-Arias, M., 2012. High novelty-seeking predicts greater sensitivity to the conditioned rewarding effects of cocaine. Pharmacology Biochemistry and Behavior 102, 124–132.

Volkow, N.D., Morales, M., 2015. The brain on drugs: from reward to addiction. Cell 162, 712–725.

Volkow, N.D., Fowler, J.S., Wang, G.J., Hitzemann, R., Logan, J., Schlyer, D.J., Dewey, S.L., Wolf, A.P., 1993. Decreased dopamine D2 receptor availability is associated with reduced frontal metabolism in cocaine abusers. Synapse 14, 169–177.

Volkow, N.D., Wang, G.J., Fowler, J.S., Gatley, S.J., Ding, Y.S., Logan, J., Dewey, S.L., Hitzemann, R., Lieberman, J., 1996. Relationship between psychostimulant-induced "high" and dopamine transporter occupancy. Proceedings of the National Academy of Sciences of the United States of America 93, 10388–10392.

Volkow, N.D., Wang, G.J., Fowler, J.S., Logan, J., Gatley, S.J., Hitzemann, R., Chen, A.D., Dewey, S.L., Pappas, N., 1997. Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subjects. Nature 386, 830–833.

Volkow, N.D., Wang, G.J., Fowler, J.S., Logan, J., Gatley, S.J., Wong, C., Hitzemann, R., Pappas, N.R., 1999. Reinforcing effects of psychostimulants in humans are associated with increases in brain dopamine and occupancy of D(2) receptors. Journal of Pharmacology and Experimental Therapeutics 291, 409–415.

Volkow, N.D., Wang, G.J., Ma, Y., Fowler, J.S., Zhu, W., Maynard, L., Telang, F., Vaska, P., Ding, Y.S., Wong, C., Swanson, J.M., 2003. Expectation enhances the regional brain metabolic and the reinforcing effects of stimulants in cocaine abusers. Journal of Neuroscience 23, 11461–11468.

Volkow, N.D., Wang, G.J., Telang, F., Fowler, J.S., Logan, J., Jayne, M., Ma, Y., Pradhan, K., Wong, C., 2007. Profound decreases in dopamine release in striatum in detoxified alcoholics: possible orbitofrontal involvement. Journal of Neuroscience 27, 12700–12706.

Volpicelli, J.R., Ulm, R.R., Hopson, N., 1990. The bidirectional effects of shock on alcohol preference in rats. Alcoholism: Clinical and Experimental Research 14, 913–916.

Walker, Q.D., Schramm-Sapyta, N.L., Caster, J.M., Waller, S.T., Brooks, M.P., Kuhn, C.M., 2009. Novelty-induced locomotion is positively associated with cocaine ingestion in adolescent rats; anxiety is correlated in adults. Pharmacology Biochemistry and Behavior 91, 398–408.

Wang, X., Mozhui, K., Li, Z., Mulligan, M.K., Ingels, J.F., Zhou, X., Hori, R.T., Chen, H., Cook, M.N., Williams, R.W., Lu, L., 2012. A promoter polymorphism in the Per3 gene is associated with alcohol and stress response. Translational Psychiatry 2, e73.

Wilhelm, C.J., Mitchell, S.H., 2008. Rats bred for high alcohol drinking are more sensitive to delayed and probabilistic outcomes. Genes, Brain and Behavior 7, 705–713.

Willner, P., Hardman, S., Eaton, G., 1995. Subjective and behavioural evaluation of cigarette cravings. Psychopharmacology (Berlin) 118, 171–177.

Wolffgramm, J., Heyne, A., 1995. From controlled drug intake to loss of control: the irreversible development of drug addiction in the rat. Behavioural Brain Research 70, 77–94.

Yamamoto, T., Nakahata, Y., Tanaka, M., Yoshida, M., Soma, H., Shinohara, K., Yasuda, A., Mamine, T., Takumi, T., 2005. Acute physical stress elevates mouse period1 mRNA expression in mouse peripheral tissues via a glucocorticoid-responsive element. Journal of Biological Chemistry 280, 42036–42043.

Zacny, J.P., Bodker, B.K., de Wit, H., 1992. Effects of setting on the subjective and behavioral effects of d-amphetamine in humans. Addictive Behaviors 17, 27–33.

Zheng, X., Ke, X., Tan, B., Luo, X., Xu, W., Yang, X., Sui, N., 2003. Susceptibility to morphine place conditioning: relationship with stress-induced locomotion and novelty-seeking behavior in juvenile and adult rats. Pharmacology Biochemistry and Behavior 75, 929–935.

Zilberman, M., Tavares, H., el-Guebaly, N., 2003. Gender similarities and differences: the prevalence and course of alcohol- and other substance-related disorders. Journal of Addictive Diseases 22, 61−74.

Zimmermann, U.S., Mick, I., Laucht, M., Vitvitskiy, V., Plawecki, M.H., Mann, K.F., O'Connor, S., 2009. Offspring of parents with an alcohol use disorder prefer higher levels of brain alcohol exposure in experiments involving computer-assisted self-infusion of ethanol (CASE). Psychopharmacology (Berlin) 202, 689−697.

Zlebnik, N.E., Anker, J.J., Carroll, M.E., 2012. Exercise to reduce the escalation of cocaine self-administration in adolescent and adult rats. Psychopharmacology (Berlin) 224, 387−400.

Chapter 32

Human Variability and the Origins and Evolution of Language

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INTRODUCTION

Since Darwin's time, the human language capacity has been a perennially cited paragon of extreme complexity. In general, evolutionary biologists assume that there is a positive correlation between the complexity of functional adaptive traits and the intensity and duration of natural selection driving their evolution. Although the role of selection is unquestionable, especially with respect to functional correspondences between an organism's adaptations and its environment, the correlation between the extent of selective "pressure" and the evolution of functional complexity is not so clear.

The recent resurgence of interest in the contribution of epigenetic processes to the course of evolutionary change, popularly known as evo-devo, has begun to focus attention on other potential sources of complex function and structure in evolution. These mostly involve the self-organizing and intra-selection processes that underlie the epigenetic processes critical for the development of much of the complex structure that constitutes animal and plant bodies. Considering the contribution of these processes for producing complex functional organization, in addition to natural selection, may be particularly informative for understanding the unusual mental capacities of humans, such as the capacity for language. This is because brain development is highly dependent upon multiple levels and phases of epigenetic processes to generate its enormous complexity. The many interdependent patterns of gene expression, stem cell proliferation, neurogenesis, apoptosis, cellular migration, axonal extension, and activity-dependent competition for synapses that interact to produce a mammal brain constitute a large repertoire of epigenetic "tools" available for evolution to modify. Particularly, then, when considering the evolution of the unique and complex neural functions that arose in human evolution, it is important to consider the contributions of these formative processes.

With respect to the evolution of the human brain and its adaptations for language, we need to confront an additional challenge. Although human brains are unusually large compared to our closest primate relatives—well beyond predictions based on allometric scaling—this is due to expansion of neural populations that have unambiguous homologs in other primates (reviewed in Deacon, 1997). In other words, no "new" brain structures evolved to support the distinctive cognitive capacities of the human species, such as language. Instead, language functions have effectively recruited older neural systems, previously adapted to serve other functions.

Although it is tempting to ignore the details and simply attribute the many cognitive differences that separate us from our ape relatives to an enlarged brain, the distinctiveness of human mentality—and especially of language—argues that they are not merely products of increased general intelligence (though a simple correlation between relative brain size and general intelligence is doubtful).

The language capacity is particularly challenging to explain because language is an emergent function, meaning that it is not some prior function just requiring fine-tuning. Our various inherited vocalizations, such as laughter, shrieks of fright, and cries of anguish, are comparatively localized in their neurological control (mostly subcortical), as are other modes of communication in animals. In comparison, language depends on a widely dispersed constellation of cortical systems, each of which can be found in other primate brains, but evolved for very different functions. These brain systems have become collectively recruited for language only because their previously

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00032-6

evolved functions overlapped significantly with some processing demand necessitated by language, though evolved for quite different functions altogether. Indeed, the neural structures and circuits involved in the production and comprehension of language are homologous to structures found ubiquitously in most monkey and ape brains: old structures performing unprecedented new tricks.

And language functions are not merely supported by a few language-specialized cortical areas. Recent in vivo imaging and physiological techniques have vastly expanded the list of cortical and subcortical brain structures involved in the production and comprehension of language. More than a dozen cortical areas in both cerebral hemispheres, and numerous subcortical nuclei have been shown to play important roles in language processing. How could these many diverse and previously distinct brain systems have become so functionally intertwined and interdependent in their contributions to this unprecedented mode of communicating?

A final mystery concerns the extent to which this dominant form of human communication depends on information maintained primarily by social transmission. Even if we accept the claims of theories postulating an innate universal grammar, still the vast quantity and high fidelity of the information constituting even a typical vocabulary stands out as exceedingly anomalous from a biological point of view. How did such a large fraction of our communicative capacity wind up being offloaded onto social transmission?

Considering the ease with which young children acquire language and the near impossibility of this for nonhuman species, there is little doubt that many features of human brain organization relevant to the language capacity have evolved under the influence of natural selection. Identifying plausible socioecological contexts that may have selectively favored the suite of adaptations relevant to language communication has been the focus of nearly all theories of human brain evolution.

As a counterpart to this literature, however, I will focus instead on the possibility that certain—perhaps crucial—contributors to this most enigmatic and diagnostic human difference may have arisen as a consequence of epigenetic constraints and biases rather than selection favoring adaptive improvement (see also Deacon, 2009, 2010). By refocusing attention on these less obvious contributions to the evolutionary process, I am not suggesting that natural selection mechanisms are inapplicable or subordinate factors in brain evolution. Only that epigenetic constraints and biases may have contributed critical formative principles that must be considered an integral component of a complete theory of brain evolution. But the effects of stabilizing selection may actually hinder the evolutionary "exploration" of alternative functional synergies, particularly those that involve synergistic interactions between previously independent adaptations. In such cases, relaxation of selection may play an important role in the evolution of complexity by enabling drift and the consequent partial degradation of epigenetic processes. This possibility will be explored later as it may apply to the evolution of the novel functional synergies underlying language.

Before exploring its possible consequences for human brain evolution, it is useful to begin with comparatively simple and well-understood processes of evolutionary changes due to relaxation of selection (eg, see Olson, 1999). I will begin by reviewing a few paradigm cases of intragenomic relaxation of selection due to gene duplication. I will then extend this analysis to explore what I will call intrasomatic relaxation of selection due to the segmental duplication of body structures. Finally, I will review examples of relaxation of selection due to extrasomatic (eg, environmental) duplication of function. These will provide a general perspective from which the possible consequences of relaxed selection on human behavior and brain evolution can be considered, with a particular emphasis on language.

LEVELS OF RELAXED SELECTION

Intragenomic Relaxed Selection

Gene duplication is a common occurrence in the evolution of genomes (Ohno, 1970; Ohta, 1994; Van de Peer et al., 2001). It is probably the major source of new genes in the course of evolution. It is also a major means by which cooperative protein complexes arise in evolution (Orgel, 1977; Zhang, 2003). Multiple occurrences of gene duplication over the course of evolution have produced "families" of structurally and functionally related genes. It may even be the case that most "new" genes arise as members of a "lineage" of genes sharing a common ancestral gene (Walsh, 1995; Zhang, 2003).

During gene duplication, a length of DNA is literally copied and spliced into the chromosome nearby, possibly as a result of uneven crossover events during meiotic replication, viral gene insertion and excision, or some other intrinsic or extrinsic mechanism that modifies gene replication. The result of such events is that a nucleotide sequence may be duplicated that contains intact regulatory and coding segments for production of a functional protein. The functional consequence is that there is now two ways of producing the same protein and its phenotypic effect. This redundancy can relax selection on the duplicate gene's function. Thus, if one of two duplicated genes acquires mutations that degrade its phenotypic function, it will not impact the reproduction of the organism (and that modified copy) so long as the other copy remains intact. Moreover, the now mutated gene can continue to acquire mutational changes, so long as its modified phenotypic effect is not

somehow deleterious. Such mutations will thus be effectively or nearly neutral.

The typical consequence of this sort of neutrality with respect to selection can be described as a "random walk" away from the original function. The result is the accumulation of arbitrary sequence changes at the genetic level and a progressively degraded or dedifferentiated contribution to the phenotype. Presumably, persistent shielding from any selection effects will eventually lead to complete loss of function, as in pseudogenes.

This has been the fate of a very large number of genes in the human genome, which were once associated with a more acute olfactory sense (eg, Rouquier et al., 1998). It is estimated that a typical mammal has on the order of 1300 genes encoding distinct olfactory receptor molecules. This number was radically reduced both in primate and in human evolution. The human species has had roughly 60% of these genes degrade to become pseudogenes (Gilad et al., 2003). This clearly reflects very weak, to nearly nonexistent, selection to maintain the numbers and diversity of these receptor molecules.

But degradation to pseudogene status is not inevitable for gene duplicates. Because gene duplication can involve an already functional segment of DNA, slight degradations of its sequence may only incrementally alter its phenotypic effects. The progressive degradation of functional specificity that is likely to result can, however, be seen as a sort of "exploration" of variants of the original function. For example, a single protein may require structural compromises to accommodate its multiple associations to other molecules, but multiple variant forms may each evolve specificity for one or another of these relationships.

In other words, the duplication, relaxation of purifying selection, and random walk that results from gene duplication can provide a kind of exploration of the space of possible synergistic relationships that can result from a sort of fractionation of existing functions. This is a recipe for increasing functional complexity (Lynch and Conery, 2003).

If the prevalence of gene duplication in animal and plant genomes is any indication, the probability that a given duplication will result in a useful fragmentation of an original function is far from zero. Gene families, consisting of many paralogous genes (eg, derived from a common ancestral gene), are widespread in complex organisms and are often responsible for similar or even synergistic phenotypic functions. To illustrate this, consider two well-known examples.

The first is the globin gene family, and specifically the hemoglobins. The hemoglobin protein complex contained in red blood cells comprises two varieties of the hemoglobin protein—alpha and beta hemoglobin—each produced by a distinct hemoglobin gene. Two alpha- and two beta-hemoglobin proteins fit together to form a tetrahedral complex made possible due to the complementary shapes of the molecular surfaces forming the interior of the tetramer with the iron-containing oxygen-binding regions occupying the "corners" of the tetrahedron. These two forms of hemoglobin arose from a gene duplication event, and the ancestral hemoglobin itself arose from duplication of an ancestral gene for both hemoglobin and myoglobin.

Changes that increased the stability of tetrameric binding of the two hemoglobin variants appear to have been favored by natural selection with respect to one another, probably because of the superior oxygen transport capacity of the tetrahedral form. In other words, in their evolutionary random walks through different three-dimensional configurations, the two "sister" versions of hemoglobin retained their oxygen-binding function while effectively "sampling" the consequences of this secondary feature of their molecular shape "explored" via sexual recombination.

This particular combination of alpha and beta hemoglobins is not, however, present at all stages of the mammalian life cycle. In the fetus of a placental mammal, additional variant beta-hemoglobin forms are expressed, three of which are termed gamma, delta, and epsilon hemoglobin. These variants are expressed at different stages of gestation, and are each coded by a different variant duplicate of the beta form of the gene, with the entire family present in a continuous segment of chromosome 11. These beta-hemoglobin duplication events, which occurred during the course of placental mammal evolution, have also given rise to two pseudo-beta hemoglobin genes, which no longer produce a corresponding protein. The remaining four beta-hemoglobin genes are expressed at slightly different times during development in the order epsilon-gamma-delta-beta.

The functional value of this is related to the fetus's need to acquire oxygen from mother's hemoglobin and yet still transfer it from blood to its own somatic cells despite changes in placentation and increasing body size. As a result, embryonic and fetal hemoglobin requires a different oxygen-binding affinity over the course of gestation. At different stages of gestation, there will be a different optimal balance of hemoglobin affinities between mother and baby. The different beta-hemoglobin variants expressed during different phases of gestation enable the fetus to progressively adapt to this challenge, until at birth beta hemoglobin becomes the predominant form produced. Analogous to the complementarity "discovered" due to alpha/beta duplication, these additional duplications of the beta-hemoglobin gene led to synergies of timing and oxygen-binding affinities that became subject to selection in the context of internal gestation.

In summary, spontaneous gene duplication results in functional redundancy, thereby reducing the intensity of purifying selection on each duplicate. Relaxation of

purifying selection allows variations to persist and accumulate in one duplicate while maintaining the original function in the other. If accumulated changes result in only modest degradation of the original functional specificity, there is a nonzero probability that pairings of duplicates will occur that complement each other's functional differences resulting in synergistic effects.

Intrasomatic Relaxed Selection

Perhaps the most dramatic example of the duplication, masking, random walk, and functional complementation effect is demonstrated by duplication of regulatory genes. One consequence of this hierarchic recursive genetic relationship is that changes in one gene can influence a large number of other genes in concert. So, the functional divergence and interaction effects that result from duplication of such regulatory genes can be global and systemic, affecting complex phenotypic traits.

The classic example of regulatory gene duplication effects involves a family of genes containing a nucleotide sequence coding for a DNA binding domain called the homeodomain. A class of such genes called homeobox genes are responsible for the large-scale segmental organization of animal body plans (independently discovered by McGinnis et al., 1984; Scott and Weiner, 1984). In the fruit fly, they are called HOM genes, and their homologs in mammals are called Hox genes (though there are a very large number of more distantly related regulatory genes as well). These underwent a number of duplications in the common ancestry, leading up to the separation of the arthropod and vertebrate lineages. Because these genes affect coordinated expression of large suites of other genes (many of which also have further regulatory functions), they play a role in producing slightly variant forms of whole body structures in these animals.

This was first demonstrated by recognizing that mutations of these genes produce systematic variations of body segments in flies, causing out-of-place expression of structures that normally are segment-specific, such as legs expressed where antennae are normally produced. The discovery that the theme-and-variation logic of the different insect body segments was correlated with the expression of different HOM gene duplicates expressed in that segment has revolutionized the study of development and served as the keystone insight solidifying the value of the evo-devo paradigm.

Because HOM/Hox gene duplication expresses itself as organ duplication, the logic of duplication, relaxed selection, divergence, and synergistic complementation is expressed above the genomic level. In arthropods such as centipedes the corresponding organs (eg, legs) of adjacent segments are highly similar, but since adjacent legs serve almost identical functions, they can also partially relax selection on the functional specificity of one another. This reduction of the effects of stabilizing selection can lead to drift of features on one segment away from those on another.

The structural–functional redundancy provided by adjacent segments minimizes the probability of catastrophic loss of function, and it also increases the likelihood that divergent but complementary functions can develop in other segments. In various arthropods, such as grasshoppers, spiders, lobsters, flies, and so forth, the different appendages with leg-like form have evolved into specialized antennae, spinnerets, claws, and many other structures sharing the same jointed architecture, but modified to serve quite distinct functions.

In each of these cases, and despite their different levels of function, the redundancy of function that results from duplications significantly reduces the improbability of evolving synergistic functional linkages. Because they share a common ancestral function, randomly variant duplicated features of an organism potentially "explore" the diverse dimensions of the original function. Their underlying commonalities also increase the probability that variant duplicates will fractionate the original function, thereby increasing the probability of producing synergistic functional consequences.

The way that the resulting functional interactions exploit combinatorial relationships that were previously hidden (or inaccessible because purifying selection constrained variation) is analogous to Conrad Waddington's logic of canalization, in which epigenetic interdependencies can emerge to become selected in their own right. Like Waddington's (1953) notion of a "phenocopy," a novel functional capacity that emerges from complementary combinatorial relationships can become selectively favored for the synergy that results. Together these effects not only "explore" adjacent functional possibilities and "capture" novel higher order synergistic relationships, but they provide an evolutionary cycle that can generate progressively more complex forms of adaptation, as each stabilized synergistic relationship can supply the substrates for new duplication effects.

Extrasomatic Relaxed Selection

Analogously, ecological and social factors can also contribute functional redundancies that relax selection on selected traits enabling them to vary away from their original specificity, potentially shifting to other related functions or losing function altogether. Because the duplicated function is in this case extrinsic to the organism, loss of an endogenous capacity requires maintaining access to this extrinsic factor that now provides it. This may result in a shift of selection in favor of any traits that aid in maintaining this relationship.

A classic example that bridges between the genetic and environmental effects of relaxed selection is the loss of the capacity to synthesize ascorbic acid (vitamin C) during the evolution of the anthropoid primates. Monkeys and apes, including humans, are among some of the very few mammals that must obtain ascorbic acid from dietary sources (Chatterjee, 1973). Most mammals synthesize their own ascorbic acid. This is the case for rats. In 1994, Japanese researchers (Nishikimi et al., 1994) sequenced the gene on chromosome 8 of the rat genome that codes for the final catalyst in the metabolic pathway that endogenously produces ascorbic acid (called l-gulano-lactone oxidase, abbreviated GULO). They then used the sequence from this gene to probe the genomes of other species, including *Homo sapiens*. What they found was surprising. Although humans are unable to synthesize their own ascorbic acid, the human genome includes a pseudogene that is homologous to the rat GULO. The GULO pseudogene in humans has accumulated considerable mutational damage, including a frame shift mutation, deletion of a number of exons, and the random insertion of "stop" codons.

This is evidence that the GULO gene in anthropoid primates has long been freed from the stabilizing influence of natural selection, and that the sequence has effectively taken a random walk, resulting in complete loss of function. So what made it functionality redundant and allowed it to degrade to this extent?

The origin of the anthropoid primates was associated with a shift from nocturnal insectivory to diurnal frugivory, as indicated by changes in the size of the orbits and a change in tooth morphology in the primate fossil record. The evolutionary implication is that at this point regular foraging on fruit introduced a semi-reliable extrinsic source of ascorbic acid into the diet. Under these conditions, selection stabilizing the function of the GULO gene would have been relaxed by this acquired behavioral adaptation and the ascorbic acid rich niche that was thereby created. The eventual complete loss of function of the GULO gene appears to have been the result, along with the need to acquire ascorbic acid through diet.

So, the relaxation of selection on this gene would have inevitably shifted selection to affect a variety of other traits that help to maintain the availability of this now essential nutrient. The capacity to judge the ripeness of fruit via the evolution of three-color vision, or to find the sugar-rich and slightly acidic content of fruit attractive due to changes in taste receptors, or to metabolize the sugars and tolerate the ethanol that ripe fruits contain might each have become important capacities subject to natural selection as a result. In this way the extrasomatic duplication and degradation of this gene's function would have shifted selection onto a diverse suite of traits that were previously unrelated to the antioxidant functions of ascorbic acid.

RELAXED SELECTION AND BRAIN EVOLUTION

Domestication and Relaxed Sexual Selection

The discontinuities between the basal forebrain and midbrain nuclei that control mammalian vocal calls and the diversely distributed cortical control of human speech and language comprehension suggest that language abilities were unlikely just the result of selection for more sophisticated vocal communication alone. Moreover, the synergistic functional interdependence among the diverse cortical systems recruited for language functions can only have been honed for its contributions to language if this synergy was already in place. It is with respect to this conundrum of accounting for the emergence of a complex novel function *before there can be selection to fine-tune it* that a consideration of relaxed selection may be helpful.

Recent investigation of a parallel shift in both complexity and neural substrate in birdsong may be able to shed some light on this. In a comparative study of a long-domesticated songbird, the Bengalese Finch, and its wild cousin, the White-Rump Munia, it was discovered that the domesticated lineage was a far more facile song-learner with a much more complex and flexible song than its wild cousin. This was despite the fact that the Bengalese Finch was bred in captivity for coloration, not singing (Okanoya, 2004). The domestic/wild difference of song complexity and song learning in these close finch breeds parallels what is found in comparisons between songbird species that are social song-learners and those that are non-learners. This difference correlates with a much more extensive neural control of song in birds that learn a complex and variable song by listening to adult singers. Despite minimal neuroanatomical differences between these breeds, the domesticate finch song depends on many more forebrain structures than does the singing of its wild cousin.

The fact that this behavioral and neural complexity can arise spontaneously without specific breeding for song complexity is a surprising finding since it is generally assumed that song complexity evolves under the influence of intense sexual selection and selection for species identification in the wild. These sources of selection would have been relaxed by domestication. One intriguing interpretation is that the relaxation of natural and sexual selection on singing paradoxically was responsible for song elaboration in Bengalese Finches. In brief, with song becoming irrelevant to species identification, territorial defense, mate attraction, predator avoidance, and so on, degrading mutations and existing deleterious alleles affecting the specification of the wild stereotypic song would not have been

weeded out. The result would likely be degradation of innate biases controlling song production.

Degradation of innate song structure constraints would result in both a more variable song and songs that are more susceptible to nongenetic influences. On the one hand, if song structure is no longer strictly controlled by motor biases and an innately pre-specified auditory song template, other linked brain systems could begin to play a biasing role in song production. With innate sensori-motor biases weakened, auditory experience, social context, learning biases, and attentional factors can all begin to influence singing. Since learning from social experience can play a much larger role in song structure once innate constraints are relaxed, a number of forebrain systems involved in motor learning (analogous to premotor cortex and striatum in mammals brains) have become involved. The result is that the domestic song is more variable, more complicated, and more influenced by social experience.

Language Analogs to the Changes in Finch Song Control

The change in song control as a result of relaxed selection in the domesticate finch is paralleled by a number of features associated with the shift from innate calls to language in the hominin lineage. Like the domesticated finch, many more brain systems influence human communicative behavior than in the communicative behaviors of our close primate relatives. Human language evolution involved a shift from largely innate subcortically mediated vocal and gestural communications to a primarily cortically mediated and more widely distributed interdependent system of brain regions. In addition, such as the finch, there has been a significant shift from a genetically constrained behavioral capacity to a comparatively flexible behavioral capacity in which a significant fraction of structural specification is socially—not genetically—transmitted.

These analogies suggest a novel approach to the riddle of explaining how language capacities could have recruited a multisystem functional synergy among cortical systems. In both cases, it seems likely that a reduction in the innate constraints affecting vocal communication has led to the involvement of previously unrelated neurological systems. Indeed, this freedom from constraint may have been an essential precondition for being able to correlate learned vocal behaviors with the wide diversity of objects, events, properties, and relationships that language is capable of referring to.

Of course the human case is unlike the finch example in a number of important respects. Most obviously, language provides a capacity for symbolic communication, whereas birdsong primarily provides indices of sex, maturity, species identity, and so forth. And, perhaps more importantly, the novel synergistic neurological relationships that support language functions have almost certainly have been subject to selection for their contribution to language and its central role in promoting cooperative social organization during recent hominin evolution. The flexible socially-acquired songs of the domesticated finch are, in contrast, not obviously subject to selection to augment and fine-tune communicative functions (though this is a topic that could be explored in future research).

Probably the clearest evidence for a relaxation effect is provided by infant babbling in humans. This unprecedented tendency to freely play with vocal sound production occurs with minimal innate constraint on what sound can follow what sound (except for physical constraints on vocal sound generation). Babbling also occurs in contexts of comparatively low arousal, whereas laughter, crying, or shrieking are each produced in comparatively specific high arousal states and with specific contextual associations. This reduction of innate arousal and contextual constraint on vocal communication opens the door for numerous other influences to begin to play a role.

Other behavioral parallels include the following: freeing vocalization from an association with specific emotional states (as remains the case of non-language communications such as laughter and sobbing); equalization of transition biases from sound to sound (also highly constrained in human innate vocalizations); an increased influence of auditory learning for vocalization, which has become an indispensable feature of human language transmission since the vocal repertoire that defines a given language is almost entirely determined by social transmission; the reduction of human innate call types and communicative specificity, along with the development of human-specific "calls" (like laughter and sobbing) and prosodic features of speech that complement the symbolic functions of language by providing emotional/arousal information.

The extensive dependency of language on socially transmitted information suggests that a significant degree of genetic control of brain development relevant to language has also likely been "offloaded" to this extrinsic source of information. This hypothesis is, of course, almost diametrically opposite to claims that the human language capacity depends on highly specialized innate constraints on possible syntactic structures, as was originally proposed by the linguist Noam Chomsky (1968). However, a significant role for loss of innate specification during the evolution of the language capacity is not inconsistent with the presence of a wide array of ancillary adaptive changes in brain function that contribute to the ease of language acquisition and use. Similar to the ancillary adaptations for color vision and taste preferences that evolved in response to primate dependence on extrinsically provided ascorbic acid, the shift to a dependence on socially transmitted vocal communication has almost certainly had secondary reorganizing effects on the evolution of many other brain functions.

Ancillary adaptations that may have evolved to help stabilize and maintain this extrinsic epigenetic information source may include an enhancement of verbal short-term memory, a more developed capacity for transfer learning, a strong predisposition to engage in vocal mimicry, enhancement of joint attention-recruitment by gaze-following and pointing behavior, and an increased capacity for empathy and for inferring the mental states of others. These and other changes in cognitive functions that support this novel communicative capacity need not be language-specific to contribute synergistically to making it a highly robust and canalized mental function. Yet, they can all be counted as part of a suite of "language adaptations." Once the reproductive advantages of symbolically transmitted knowledge and social organization became reliable, there would certainly have been selection favoring not only the stabilization of this unprecedented neural synergy but selection favoring any of these ancillary traits that could help to optimize language acquisition and function. Seen from this vantage point, many converging factors appear likely to have played a formative role in the evolution of this unique social-cognitive-biological phenomenon once this novel synergy became available.

CONCLUSIONS AND POSSIBLE IMPLICATIONS

So what follows from the possibility that the unique combination of traits that support our language capacities and our dependence on social transmission are consequences of both relaxed selection and shift of selective pressure onto new functions? Considering the possibility of a significant role for relaxed selection in our evolutionary past forces us to consider that we may not be genetically augmented apes with numerous genetic and neural improvements that make us better than our cousins. It suggests rather that many features we have considered adaptive "improvements" might better be understood as consequences of degenerative processes producing greater flexibility and less dependence on genetic control.

For paleontologists, geneticists, and anthropologists, this analysis also poses some interesting new research questions. What conditions or circumstances in hominin evolution could have been the source for relaxation of selection leading to this shift of function? What sort of genetic evidence is there to support relaxation of selection rather than increased directional selection on language functions? And what might be the secondary consequences of an evolutionary past characterized by extensive relaxation of selection and the offloading of once innate capacities onto social transmission processes?

In the case of the domesticated finch, the shift in neurological control of vocalization and the offloading of control of song structure to social transmission processes is hypothesized to be the result of relaxation of sexual selection. Evidence for a major shift in the role of sexual selection in hominin evolution is provided by the significant reduction in sexual dimorphism in body size during the transition from *Australopithecus* to *Homo*. This roughly followed the emergence of the first Oldowan stone tool technology two and a half million years ago, as well as the first significant increase in relative brain size above typical ape levels. In my 1997 book, *The Symbolic Species*, I argued that foraging for animal remains with stone tools required a form of cooperative behavior that was able to control the intrinsically disruptive innate predispositions associated with mate competition and offspring care. Offloading some degree of control over these social-sexual behaviors onto socially transmitted constraints would thereby have initiated a phase of relaxed sexual selection.

There is also genetic evidence for relaxed selection in our lineage. For example, in an analysis of nearly 14,000 loci, Bakewell et al. (2007) found that more genes underwent positive selection in chimpanzee evolution than in human evolution, and that "… despite a generally higher nonsynonymous substitution rate in humans… these observations are explainable by the reduced efficacy of natural selection in humans." Wang et al. (2006) identified "… 80 nonprocessed pseudogenes that were inactivated in the human lineage after its separation from the chimpanzee lineage." They find that some of these loss-of-function effects have been subject to positive selection and speculate on the way these losses may be supportive of a "less-is-more" adaptive response. And McLean et al. (2011) reported that there has been extensive human-specific loss of non-coding regulatory regions of the human genome that are highly conserved in chimpanzees and other mammals. They identify 511 such deletions in humans that are enriched near genes associated with hormonal and neural functions, and which are distributed across all human chromosomes (with the exception of the Y chromosome). This suggests that there has been a significant loss and/or shift of regulatory control within the human genome as compared to our primate and mammal relatives. These findings are suggestive evidence for widespread relaxation of selection in the human lineage. It is particularly interesting from our perspective to note that a large fraction of these deletions are associated with genes involved in hormonal and neurological functions.

Finally, considering the synergistic consequences of intrasomatic relaxed selection effects due to organ-level duplication, discussed earlier, it is not unreasonable to suggest that human cortical expansion itself may have contributed to a relaxation-synergy effect. Increase in cortical area sizes could have enabled a related form of functional duplication that enabled increased fractionation and diversification of existing functions without loss of

processing efficiency. This too could have been an aid to the evolution of novel synergistic linkages among cortical functions along with increased flexibility and variability. In this respect, there is also recent evidence for relaxed genetic control of cortical organization in human brains compared with chimpanzees (eg, Gómez-Roblesa et al., 2015).

Would it be too humbling to see ourselves as somewhat genetically degenerate, neurologically dedifferentiated apes? Reframing humanness in biologically degenerate terms does not, as we have shown, deny that we are in many respects more complex, both neurologically and behaviorally than other ape species. Moreover, the dedifferentiating effects of relaxed selection may help to explain certain other enigmatic features of human nature, such as our susceptibility to manipulation by symbolic influences instilled by religious and cultural traditions. For example, the nearly universal determination of human reproductive arrangements and mate choice by cultural tradition and kinship agreements suggests that even a considerable fraction of control over our social-sexual behaviors has been offloaded to socially transmitted symbolic processes.

REFERENCES

Bakewell, M., Shi, P., Zhang, J., 2007. More genes underwent positive selection in chimpanzee evolution than in human evolution. PNAS 104, 7489–7494.

Chatterjee, I.B., 1973. Evolution and the biosynthesis of ascorbic acid. Science 182, 1271–1272.

Chomsky, N., 1968. Language and Mind. Harcourt Brace Jovanovich, Inc., New York.

Deacon, T., 1997. The Symbolic Species: The Coevolution of Language and the Brain. W. W. Norton & Co, New York.

Deacon, T., 2009. Relaxed selection and the role of epigenesis in the evolution of language. In: Blumberg, M.S., Freeman, J.H., Robinson, S.R. (Eds.), Oxford Handbook of Developmental Behavioral Neuroscience.

Deacon, T., 2010. A role for relaxed selection in the evolution of the language capacity. PNAS 107, 9000–9006.

Gilad, Y., Man, O., Paabo, S., Lancet, D., 2003. Human specific loss of olfactory receptor genes. PNAS 100, 3324–3327.

Gómez-Robles, A., Hopkins, W.D., Schapiro, J., Sherwood, C.C., 2015. Relaxed genetic control of cortical organization in human brains compared with chimpanzees. PNAS 112, 14799–14804.

Lynch, M., Conery, J.S., 2003. The origin of genome complexity. Science 302, 1401–1404.

McGinnis, W., Levine, M.S., Hafen, E., Kuroiwa, A., Gehring, W.J., 1984. A conserved DNA sequence in homoeotic genes of the *Drosophila* Antennapedia and bithorax complexes. Nature 308, 428–433.

McLean, C.Y., Reno, P.L., Pollen, A.A., Bassan, A.I., Capellini, T.D., et al., 2011. Human-specific loss of regulatory DNA and the evolution of human-specific traits. Nature 471, 216–219.

Nishikimi, M., Fukuyama, R., Minoshima, S., Shimizu, N., Yagi, K., 1994. Cloning and chromosomal mapping of the human nonfunctional gene for L-gulono-gammalactone oxidase, the enzyme for L-ascorbic acid biosynthesis missing in man. The Journal of Biological Chemistry 269, 13685–13688.

Ohno, S., 1970. Evolution by Gene Duplication. Springer, Berlin.

Ohta, T., 1994. Further examples of evolution by gene duplication revealed through DNA sequence comparisons. Genetics 138, 1331–1337.

Okanoya, K., 2004. The Bengalese Finch: a window on the behavioral neurobiology of birdsong syntax. Annals of the New York Academy of Sciences 1016, 724–735.

Olson, M.V., 1999. When less is more: gene loss as an engine of evolutionary change. The American Journal of Human Genetics 64, 18–23.

Orgel, L.E., 1977. Gene duplication and the origin of proteins with novel functions. Journal of Theoretical Biology 67, 773.

Rouquier, S., Taviaux, S., Trask, B., Brand-Arpon, V., van den Engh, G., et al., 1998. Distribution of olfactory receptor genes in the human genome. Nature Genetics 18, 243–250.

Scott, M.P., Weiner, A.J., 1984. Structural relationships among genes that control development: sequence homology between the Antennapedia, Ultrabithorax, and fushi tarazu loci of *Drosophila*. PNAS 81, 4115–4119.

Van de Peer, Y., Taylor, J.S., Braasch, I., Meyer, A., 2001. The ghost of selection past: rates of evolution and functional divergence of anciently duplicated genes. Journal of Molecular Evolution 53, 436–446.

Waddington, C.H., 1953. Genetic assimilation of an acquired character. Evolution 7, 118–126.

Walsh, J.B., 1995. How often do duplicated genes evolve new functions? Genetics 139, 421–428.

Wang, X., Grus, W.E., Zhang, J., 2006. Gene losses during human origins. PloS Biology 4, 366–377.

Zhang, J., 2003. Evolution by gene duplication: an update. Trends in Ecology & Evolution 18, 292–298.

Chapter 33

Human Evolution and Progress

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INTRODUCTION

Progress presents itself as an obvious attribute of the evolutionary process. Early organisms that lived on earth were no more complex than some bacteria, archaea, and blue-green algae. Three billion years later, their descendants include orchids, bees, peacocks, and human beings, which appear to be more complex, advanced, or progressive than their primitive ancestors.

Upon reflection the issue becomes less obvious, because what do we mean when we say there has been progress in the evolutionary process? Some evolutionary lineages do not appear progressive at all: living bacteria are not very different from their ancestors of two or three billion years earlier. In addition, extinction can hardly be progressive; yet, most evolutionary lineages have become extinct. Still more, organisms may be more progressive than others with respect to some features but not with respect to other features. For example, bacteria are able to synthesize all their own components and obtain the energy they need for living from inorganic compounds; human beings depend on other organisms.

Aristotle and other philosophers of classical Greece put forward the notion that living organisms can be classified in a hierarchy going from lower to higher forms. A similar view is implicit in the Bible. The creation of the world as described in the book of Genesis contains the explicit notion that some organisms are higher than others, and it implies that living things can be arranged in a sequence from the lowest to the highest, which is man. The Bible's narrative of the creation reflects the common sense impression that earthworms are lower than fish and birds, and the latter lower than man. The idea of a "ladder of life" rising from amoeba to man is present, explicitly or implicitly, in all pre-evolutionary biology (Lovejoy, 1960 [1936]).

The theory of evolution adds the dimension of time and genetic continuity, or history, to the hierarchical classification of living things. The transition from bacteria to humans could now be seen as a natural, progressive development through time from simple to gradually more complex organisms. The expansion and diversification of life could also be judged as progress; some form of advance seems obvious in the transition from one or only a few kinds of living things to the several million species living today.

The idea of progress, applied to human history or to the world of nature, does not appear until the Renaissance. The philosophers of ancient Greece, including Aristotle, saw the world in terms of eternal cycles. It is only in the 16th century that appear the first ideas about the possibility of progress in the history of the world and of humankind. The idea of progress, associated to the increase in knowledge, becomes first entertained at that time. The idea of progress becomes associated with the notions of change, development, or direction (Bury, 1932).

THE LADDER OF LIFE

Aristotle (384–322 BCE) is fittingly recognized as one of the great philosophers of Greek Antiquity, known for his works on logic, epistemology, metaphysics, ethics, and politics. He qualifies as well as a great scientist, the first biologist in the history of the world, who dissected a variety of animals and described in detail the development of the chicken embryo from egg to hatching. During his three years in the Aegean island of Lesbos (345–342) he investigated all sorts of marine and lacustrine organisms, from coral reefs and mollusks to fish, as well as land animals. In his numerous zoological works, such as *The Generation of Animals* and others, Aristotle mentions 500 animal species, a large number relatively to the knowledge

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00033-8

of the time (Leroi, 2014). Aristotle developed a system of classification of animals, recognizing nine groups included in two large categories: animals with blood and without blood. He classified the animals with blood into five groups: mammals, birds, amphibians, reptiles, and fishes and divided the animals without blood into cephalopods, crustaceans, insects, and a fourth group that would include the rest of the animals. Aristotle's classification compares favorably with the classification by Linnaeus, 21 centuries later, who recognized only six kinds of animals: mammals, birds, reptiles, fishes, insects, and worms. Aristotle considered some animals more complex or more advanced than others, but he believed in the immutability of species, not in their evolution, and thus he did not see the difference between lower and higher animals as the outcome of a process of change or progress over time.

Among the philosophers of ancient Greece, some traces of evolutionary thinking can be found in Anaximander (610−c.547 BCE), who proposed that animals could be transformed from one kind into another, but without implying that the changes would represent advancement or what we might now call progress. A shadow of natural selection can be imagined in Empedocles (490−430 BCE), who speculated that animals would be made up of various combinations of preexisting parts, so that successful combinations would result in the animals we know, while unsuccessful ones would not persist.

Judaism, Christianity, and Islam account for the origin of the world as the handiwork of an omniscient God. The Bible speaks of higher and lower organisms and manifests humans at the top of all living organisms. Some early church fathers, like Gregor of Nazianzus (c.329−390) and Augustine (354−430) maintained that not all species of plants and animals were created as such by God; rather, some had developed in historical times from creatures created earlier by God. Their motivation was not scientific but religious. Some species may have come into existence only after the Noachian flood because it would have been impossible to hold representatives of all species in a single vessel, such as Noah's Arch.

Aristotle's notion that there is a sort of a natural ladder, a gradual succession of increasing complexity in the living world, from plants to animals to humans, was elaborated by Albert Magnus, around 1260, "the first modern European to study Aristotle's zoology" (Leroi, 2014, p. 276). Albert's notion that nature proceeds by small steps became commonplace by the early 17th century and prevailed into the 18th century. It became for Linnaeus in his *Philosophia botanica* of 1751 a methodological principle: *natura non facit saltum*, that is, nature does not make jumps. The notion that there is a Ladder of Nature or Chain of Being became temporalized, according to Arthur O. Lovejoy, and "must perforce be reinterpreted so as to admit of progress in general" (Lovejoy, 1960 [1936], p. 246).

THE IDEA OF PROGRESS

In the 17th century, Francis Bacon (1561−1626) formulated a program for the advancement of knowledge, the notion that progress in knowledge could contribute to improve the human condition. The true purpose of knowledge, according to Bacon, was to improve human life, to provide new inventions and developments, and in the case of the natural sciences, to define the supremacy of human life over the rest of nature. The true purpose of knowledge is not to pleasure the mind, or to establish the superiority of some individuals over others, their reputation, or power, but rather to advance the benefit, power, and domain of humanity over the rest of the universe. Bacon advances a notion of progress focused upon the human capacity to advance knowledge that would serve for mankind's benefit. Starting with the evidence provided by our senses, and taking advantage of technological developments, Bacon thought that knowledge could become increasingly more certain. The purpose of technology is to increase human knowledge and thus contribute to mankind's progress. These ideas would become the core of a general doctrine of progress that would be developed over the ensuing centuries (Ruse, 1996).

The Aristotelian and traditional notion that organisms can be classified in a hierarchy from lower to higher becomes further entrenched in the 17th and 18th centuries: the notion of a *scala naturae*, ranging from the inanimate world to the lower and then the higher animals and humans (Lovejoy, 1936). The chain of being is, nevertheless, perceived as static, that it was created as perfect so that any modification would be considered as harm or deterioration. Gradually, however, in the late 18th to early 19th century the notion of human progress—epitomized by Condorcet's *Sketch for a Historical Picture of the Progress of the Human Mind* (1795) in France, Adam Smith's *The Wealth of Nations* (1776) in Britain, and G.W.F. Hegel's *Philosophy of Nature* (1817) in Germany—became extended to the world of life, so that some organisms are considered more advanced or more progressive than others.

Progress as an attribute of the living world reaches an early climax with the publication in 1809 of *Philosophie Zoologique*, ("Philosophical Zoology") by the great French naturalist Jean-Baptiste Lamarck (1744−1829). Lamarck proposed the first broad theory of evolution: progress as an immanent attribute of the evolutionary process. Organisms evolve through eons of time from lower to higher forms, a process still going on and always culminating in human beings. As organisms become adapted to their environments through their habits, modifications occur. Use of an organ or structure reinforces it; disuse leads to obliteration. The characteristics acquired by use and disuse would be inherited. Organisms repeatedly evolve in a fixed sequence

of progressive transitions. Today's worms will advance gradually, always eventually culminating in human beings.

The notion that evolution is always progressive is not part of Darwin's theory of evolution by natural selection. Darwin knew that numerous species became extinct, without leaving descendants, and that many others have not changed for eons of time. "Some of the most ancient Silurian animals, as the Nautilus, Lingula, etc., do not differ much from living species; and it cannot on my theory be supposed, that these old species were the progenitors of all the species of the orders to which they belong, for they do not present characters in any degree intermediate between them" (Darwin, 1859, p. 306). Notable proponents of evolutionary progress included Ernst Haeckel, *The Evolution of Man* (1896, and Fig. 33.1) and Herbert Spencer, "Progress: its law and cause" (1852) and *First Principles* (1862; see also Richards, 1988).

DEFINITION OF PROGRESS

The meaning of statements like "Progress has occurred in the evolutionary sequence leading from bacteria to humans" or "The evolution of organisms is progressive" is not immediately obvious. Such expressions may simply mean that evolutionary sequences have a time direction, or even more simply that they are accompanied by change. The term "progress" may be clarified by comparing it with other related terms used in biological discourse. These terms are "change," "evolution," and "direction."

The term "change" means alteration, whether in the position, the state, or the nature of a thing. Progress implies change, but not vice versa; not all changes are progressive. The molecules of oxygen and nitrogen in the air of a room are continuously changing positions, but such changes would not generally be regarded as progressive. The mutation of a gene from a functional allelic state to a nonfunctional one is a change, but definitely not a progressive one.

"Evolution" and "progress" can also be distinguished, although both imply that sustained change has occurred. Evolutionary change is not necessarily progressive. The evolution of a species may lead to its own extinction, a change that is not progressive, at least not for that species. Progress can also occur without evolutionary change. Assume that in a given region of the world the seeds of a certain species are dormant because of a prolonged drought; after a burst of rain the seeds germinate and give origin to a population of plants. This change might be labeled progressive for the species, even though no evolutionary change need to have taken place.

The concept of "direction" implies that a series of changes have occurred that can be arranged in a linear sequence so that elements in the later part of the sequence are further from early elements of the sequence than intermediate elements are. Directional change may be uniform or not, depending whether every later member of the sequence is further displaced than every earlier member ("uniform" change), or whether directional change occurs only on the average ("net" change). Nonuniform or net (see later) directional change occurs when the direction of change is not constant; some elements in the sequence may represent a change of direction with respect to the immediately previous elements, but later elements in the sequence are displaced further than earlier ones on the average.

"Directionality" is sometimes equated with "irreversibility" in discussions of evolution: the process of evolution is said to have a direction because it is irreversible. Biological evolution is irreversible (except perhaps in some trivial sense, as when a previously mutated gene mutates back to its former allelic state; or when a gene increases in frequency for some time, but decreases in later generations). Direction, however, implies more than irreversibility. Consider a new pack of cards with each suit arranged from ace to ten, then knave, queen, king, and with the suits arranged in the sequence of spades, clubs, hearts, and diamonds. If we shuffle the cards thoroughly, the order of the cards will change, and the changes will be irreversible by shuffling. We may shuffle again and again until the cards are totally worn out, without ever restoring the original sequence. The change of order in the pack of cards is irreversible but not directional.

Directional changes occur in the inorganic as well as the organic world. The second law of thermodynamics, which applies to all processes in nature, describes sequential changes that are directional, and indeed, uniformly directional. Within a closed system, entropy always increases; that is, a closed system passes continuously from less probable to more probable states. The concept of direction applies to what in paleontology are called "evolutionary trends." A trend occurs in a phylogenetic sequence when a feature persistently changes through time in the members of a sequence. Trends are common occurrences in all fossil sequences that are sufficiently long to be called "sustained" (Simpson, 1953).

The concept of direction and the concept of progress are distinguishable. Consider the trend in the evolutionary sequence from fish to man toward a gradual reduction in paleontological time of the number of dermal bones in the skull roof, or the trend toward increased molarization in the last premolar that occurred in the phylogeny of the *Equidae* from the early Eocene (*Hyracotherium*) to the early Oligocene (*Haplohippus*). These trends indeed represent directional change, but it is not obvious that they should be labeled progressive; to do this, we would have to agree that the directional change had been for the better in some sense. That is, to consider a directional sequence progressive, we need to add an evaluation, namely that the

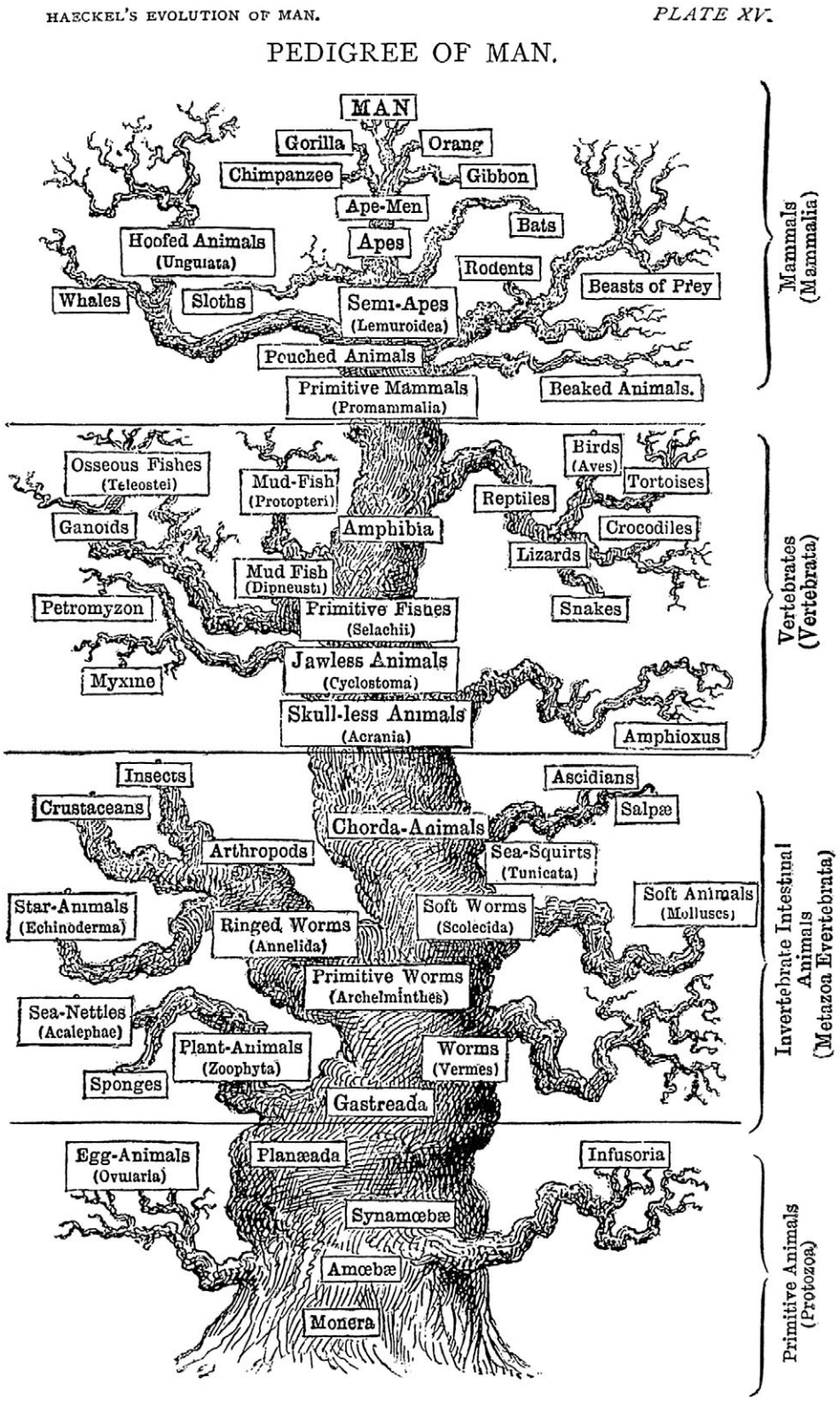

FIGURE 33.1 Ernst Haeckel's (1834–1919) tree of life showing a *scala naturae* from protozoa to mammals, with humans at the apex (1896, vol. 2, p. 188).

condition of the latter members of the sequence represents, according to some standard, a melioration or improvement. The directionality of the sequence can be recognized and accepted without any such evaluation being added. Progress implies directional change, but not vice versa.

Evolution, direction, and progress all imply a historical sequence of events that exhibit a systematic alteration of a property or state of the elements in the sequence. Progress occurs when there is directional change toward a better state or condition. The concept of progress, then, contains two elements: one descriptive, that directional change has occurred; the other axiological (=evaluative), that the change represents betterment or improvement (Ayala, 1988, 2000). Gould (1988) has argued that the idea of progress should be replaced by an "operational notion of directionality," so that the evaluative component be avoided.

The notion of progress requires that a value judgment be made about what is better and what is worse, or what is higher and what is lower, according to some axiological standard. But contrary to the belief of some authors (Ginsberg, 1944; Lewontin, 1968), the axiological standard of reference need not be a moral one. Moral progress is possible, but not all forms of progress are moral. The evaluation required for progress may be one of better versus worse, or higher versus lower, but not necessarily one of right versus wrong. "Better" may simply mean more efficient, more abundant, or more complex, without connoting any reference to moral values or standards.

One may, then, define progress as "systematic change in a feature belonging to all the members of a sequence in such a way that posterior members of the sequence exhibit an improvement of that feature." More simply, it can be defined as "directional change toward the better." Similarly, regress or retrogression is directional change for the worse. The two elements of the definition, namely directional change and improvement according to some standard, are jointly necessary and sufficient for the occurrence of progress.

Directional change, as well as progress, may be observed in sequences that are spatially rather than temporally ordered. Clines are examples of directional change recognized along a spatial dimension. In evolutionary discourse, however, historical sequences are of greatest interest.

KINDS OF PROGRESS

To seek further clarification of the concept of progress and its application in evolutionary biology, it is necessary to distinguish among various kinds of progress. This can be accomplished according to either one of the two essential elements of the definition. I shall later refer to types of progress differentiated on the basis of axiological standards of reference. Now, I shall make two distinctions that relate to the descriptive element of the definition, that is, the requirement of directional change. The first distinction takes into account the *continuity* of the direction by distinguishing between "uniform" and "net" progress. The second distinction refers to the *scope* of the sequence considered and differentiates between "general" and "particular" progress.

Uniform progress takes place whenever every later member of the sequence is better than every earlier member of the sequence according to a certain feature. This may be formally stated as follows. Let m_i be the members of the sequence, temporally ordered from 1 to n, and let p_i measure the state of the feature under evaluation. There is uniform progress if it is the case for every m_i and m_j that $p_j > p_i$ for every $j > i$.

Net progress does not require that every member of the sequence be better than all previous members of the sequence and worse than all its successors; it requires only that later members of the sequence be better, *on the average*, than earlier members. Net progress allows for temporary fluctuations of value. Formally, if the members of the sequence, m_i, are linearly arranged over time, net progress occurs whenever the regression (in the sense used in mathematical sequences) of p on time is significantly positive. Some authors have argued that progress has not occurred in evolution because no matter what standard is chosen, fluctuations can always be found in every evolutionary lineage. This argument is valid against the occurrence of uniform progress, but not against the existence of net evolutionary progress.

Notice also that neither uniform nor net progress requires that progress be unlimited, or that any specified goal will be surpassed if the sequence continues for a sufficiently long period of time. Progress requires a gradual improvement in the members of the sequence, but the rate of improvement may decrease with time. According to the definition given here, it is possible that the sequence tends asymptotically toward a definite goal, which is continuously approached but never reached.

The distinction between uniform and net progress is similar but not identical to the distinction between uniform and perpetual progress proposed by Broad (1925) and Goudge (1961). Perpetual progress, as defined by Broad, requires that the maximum of value increases, and the minimum does not decrease with time. In the formulation given earlier, Broad's perpetual progress requires that for every m_i there is at least one m_j $(j > i)$ such that $p_j > p_i$. This definition has the undesirable feature of requiring that the first element of the sequence be the worst one and the last element the best one. Neither of these two requirements is made in my definition of net progress. Also the term "perpetual" has connotations that are undesirable in the discussion of progress. The distinction between uniform and net progress is made implicitly, although never

formally stated, by Simpson (1949), who applies terms like "universal," "invariable," "constant," and "continuous" to the kind of progress that I have called uniform (although he also uses these terms with other meanings).

With respect to the scope of the sequence considered, progress can be either general (or universal) or particular. *General* (or *universal*) *progress* is that which occurs in all historical sequences of a given domain of reality and from the beginning of the sequences until their end. *Particular progress* is that which occurs in one or several but not all historical sequences, or that which takes place during part but not all of the duration of the sequences.

General progress would have occurred in evolution only if there were some feature or standard according to which progress can be predicated of the evolution of all life from its origin to the present. If progress is predicated of only one or several, but not all, lines of evolutionary descent, it is a particular kind of progress. Progress that embraces only a limited span of time from the origin of life to the present is also a particular kind of progress.

Some writers have denied that evolution is progressive on the grounds that not all evolutionary lineages exhibit advance. Some evolutionary lineages, like those leading to certain parasitic forms, are retrogressive by certain standards; and many have lineages that have become extinct without issue. These considerations are valid against a claim of general progress, but not against claims of particular forms of progress.

PROGRESS AS A BIOLOGICAL CONCEPT

I have argued that the notion of progress is axiological, and therefore, it cannot be a strictly scientific term: value judgments are not part and parcel of scientific discourse, which is characterized by empirically testable hypotheses and objective descriptions. Some authors have claimed, however, that there are biological criteria of progress that are "objective" and do not involve value judgments. I will briefly review the efforts in this regard of three distinguished biologists: J.M. Thoday, M. Kimura, and J.S. Huxley.

Thoday (1953, 1958) has pointed out the obvious fact that survival is essential to life. Therefore, he argues, progress is the increase in fitness for survival, "provided only that fitness and survival be defined as generally as possible." According to Thoday, fitness must be defined in reference to groups of organisms that can have common descendants; these groups he calls "units of evolution." A unit of evolution is what population geneticists call a Mendelian population; the most inclusive Mendelian population is the species. The fitness of a unit of evolution is defined by Thoday as "the probability that such a unit of evolution will survive for a long period of time, such as 10^8 years, that is to say will have descendants after the lapse of that time." According to Thoday, evolutionary changes, no matter what other results may have been produced, are progressive only if they increase the probability of leaving descendants after long periods of time. He correctly points out that this definition has the advantage of not assuming that progress has in fact occurred, an assumption that vitiates other attempts to define progress as a purely biological concept.

The definition of progress given by Thoday has been criticized because it apparently leads to the paradox that progress is impossible, in fact, that regress is necessary since any group of organisms will be more progressive than any of their descendants. Assume that we are concerned with ascertaining whether progress has occurred in the evolutionary transition from a Cretaceous mammal to its descendants of 100 million (10^8) years later. It is clear that if the present-day mammal species has a probability, P, of having descendants 10^8 years from now, the ancestral mammal species will have a probability no smaller than P of leaving descendants after 2×10^8 years from the time of their existence (Ayala, 1969). The probability that the ancestral species will leave descendants 2×10^8 years after their existence will be greater than P if it has any other living descendants besides the present-day mammal with which we are comparing it. As Thoday (1970) himself has pointed out, such criticism is mistaken, since it confuses the probability of survival with the fact of survival. The a priori probability that a given species will have descendants after a given lapse of time may be smaller than the a priori probability that any of its descendants will leave progeny after the same length of time.

There is, however, a legitimate criticism of Thoday's definition of progress, namely, that it is not operationally valid. Suppose that we want to find out whether one of today's mammal species is more progressive than its Cretaceous ancestor. We should have to estimate, first, the probability that today's mammal will leave descendants after a given long period of time; then, we should have to estimate the same probability for the Cretaceous species. Thoday has enumerated a variety of components that contribute to the fitness of a population as defined by him. These components are adaptation, genetic stability, genetic flexibility, phenotypic flexibility, and the stability of the environment. But it is by no means clear how these components could be quantified nor by what sort of function they could be integrated into a single parameter. In any case, there seems to be no conceivable way in which the appropriate observations and measurements could be made for the ancestral species. Thoday's definition of progress is extremely ingenious, however, it lacks operational validity. If we accept his definition, there seems to be no way in which we could ascertain whether progress has occurred in any one line of descent or in the evolution of life as a whole.

Another attempt to consider evolutionary progress as a purely biological notion has been made by Motoo Kimura (1961), by defining biological progress as an increase in the amount of genetic information stored in the organism. This information is encoded, at least for the most part, in the DNA of the nucleus. The DNA contains the information that in interaction with the environment directs the development and behavior of the individual. By making certain assumptions, Kimura has estimated the rate at which genetic information accumulates in evolution. He calculates that in the evolution of "higher" organisms genetic information has accumulated from the Cambrian to the present at an average of 0.29 *bits* per generation.

This method of measuring progressive evolution by the accumulation of genetic information is vitiated by several flaws. First, since the average rate of accumulation of information is allegedly constant per *generation*, it follows that organisms with a shorter generation time will have accumulated more information, and therefore are more progressive than organisms with a longer generation time. The evolution of mice, moles, and bats would necessarily be more progressive than horses, whales, and humans. A second flaw is that Kimura is not measuring how much genetic information has been accumulated in any given organism. Rather, he assumes that genetic information gradually accumulates with time and he then proceeds to estimate the rate at which genetic information could have accumulated. The assumption that more recent organisms have more genetic information and that, therefore, they are more progressive than their ancestors is unwarranted, and it completely invalidates Kimura's attempt to measure evolutionary progress. There is, at least at present, no way of measuring the amount of genetic information present in any one organism. Finally, the decision to consider the accumulation of genetic information as progressive requires a value judgment; it is not a biologically compelling notion.

Julian Huxley (1942, 1953) has argued that the biologist should not attempt to define progress a priori, but rather he should "proceed inductively to see whether he can or cannot find evidence of a process which can be legitimately called progressive." He believes that evolutionary progress can be defined without any reference to values. Huxley proposes first to investigate the features that mark off the "higher" from the "lower" organisms. Any evolutionary process is considered progressive in which the features that characterize higher organisms are achieved. But Huxley, like Kimura, assumes that progress has in fact occurred, and that certain living organisms, especially humans, are more progressive than others. Classifying organisms as "higher" or "lower" requires an evaluation. Huxley has not succeeded in avoiding reference to an axiological standard. The terms that he uses in his various definitions of progress, like "improvement," "general advance," "level of efficiency," etc., are all in fact evaluative.

IS EVOLUTION UNIVERSALLY PROGRESSIVE?

No attempt to define progress as a purely biological concept has succeeded. This is understandable in view of the analysis of the concept that I developed earlier. The concept of progress is evaluative and, hence, one cannot ascertain whether progress has occurred without first choosing a standard against which progress or improvement will be assessed. Two decisions are required. First, we must choose the objective feature according to which the events of objects are to be ordered. Second, a decision must be made as to what pole of the ordered elements represents improvement. These decisions involve a subjective element, but they should not be arbitrary. Biological knowledge should guide them. There is a criterion by which the validity of a standard of reference can be judged. A standard is valid if it enables us to say illuminating things about the evolution of life. How much of the relevant information is available, and whether the evaluation can be made more of less precisely, should also influence the choice of values.

It is fairly apparent that there is no standard by which *uniform* progress can be said to have taken place in the evolution of life. Changes in direction, slackening, and reversals have occurred in all evolutionary lineages, no matter what features are considered (Simpson, 1949, 1953). The question, then, is whether *net* progress has occurred in the evolution of life and in which sense.

The next question is whether there is any criterion of progress by which net progress can be said to be a general feature of evolution; or whether identifiable progress applies only to particular lineages or in particular periods. One conceivable standard of progress is the increase in the amount of genetic information stored in the organisms (Kimura, 1961). Net progress would have occurred if organisms living at a later time would have, on the average, a greater content of genetic information than their ancestors. One difficulty, insuperable at least for the present, is that there is no way in which the genetic *information* present in an organism can be measured. We could choose the Shannon−Weaver solution, as Kimura (1961) has done, by regarding all the DNA of an organism as a linear sequence of messages made up of groups of three-letter words (the codons) with a four-letter alphabet (the four DNA nucleotides). But the amount of information is not simply related to the amount of DNA, since we know that many DNA sequences are repetitive, and even much of the nonrepetitive DNA may not store information in the nucleotide sequence. In any case, what we know about the size of the genome in organisms makes it unlikely that increase of genetic information could be a general feature of the evolution of life.

However, the accumulation of the genetic information as a standard of progress can be understood in a different

way. Progress can be measured by an increase in the *kinds* of ways in which the information is stored and as an increase in the *number* of different messages encoded. Different species represent different kinds of messages; individuals are messages or units of information. Thus understood, whether an increase in the amount of information has occurred reduces to the question of whether life has diversified and expanded. This has been recognized by Simpson (1949) as the standard by which, what I call general progress, has in fact occurred in the evolution of life. According to Simpson, we can find out about evolution as a whole whether there has been a "tendency for life to expand, to fill in all the available spaces in the livable environments, including those created by the process of that expansion itself."

There are at least four different though related criteria by which the expansion of life can be measured: (1) expansion in the number of kinds of organisms, that is, the number of species, (2) expansion in the number of individuals, (3) expansion in the total bulk of living matter, and (4) expansion in the total rate of energy flow. Increases in the number of individuals or of their bulk may be a mixed blessing, as it is the case now for the human species, but they can be a measure of biological success. By any one of the four standards of progress enumerated, it appears, according to Simpson (1949), that net progress has been a general feature of the evolution of life.

Reproduction provides organisms with the potentiality to multiply exponentially: each organism is capable of producing, on the average, more than one progeny throughout its lifetime. The actual rate of increase in numbers is a net result of the balance between the rate of births and the rate of deaths of the population. In the absence of environmentally imposed restrictions, that balance is positive; populations have an intrinsic capacity to grow ad infinitum. Since the ambit in which life can exist is limited, and since the resources to which a population has access are even more limited, the rate of expansion rapidly decreases to zero, or becomes negative, or alternates between positive and negative periods.

The tendency of life to expand encounters constraints of various sorts. The expansion is limited by the environment in at least two ways. First, the supply of resources accessible to the organisms is limited. Second, favorable conditions necessary for multiplication do not always occur. Predators, parasites, and competitors, together with the various parameters of the environment embodied by the term "weather," are the main factors interfering with the multiplication of organisms even when the resources are available. Drastic and secular changes in the weather, as well as geological events, lead at times to vast decreases in the size of some populations and even the whole of life. Because of these constraints, the tendency of life to expand has not always succeeded. Nevertheless, it appears certain that life has, on the average, expanded throughout most of its history.

About 1.5 million species now living have been described and named. Current estimates place the number of living species between 5 and 30 million, with most of the unidentified animal species being beetles and other insects. Although it is difficult to estimate the number of plant species that existed in the past (since well-preserved plant fossils are rare), the number of animal species can be roughly estimated. Approximately 150,000 animal species live in the seas today, probably a larger number than the total number that existed in the Cambrian (say, about 500 million years ago) when no animal or plant species lived on the land. Animal life on land began in the Devonian (some 400 million years ago). The number of animal land species is probably at a maximum now, even if we exclude insects. Insects make up about three-quarters of all known animal species, and about half of all species if plants are included. Insects did not appear until the early Carboniferous, some 350 million years ago. The number of living insect species has become probably greater in recent times (before the Anthropocene extinctions) than it ever was before. It seems likely that, at least on the average, a gradual increase in the number of species has characterized the evolution of life (Simpson, 1949, 1953).

The number of species expands by a positive feedback process. The greater the number of species, the greater the number of environments that are created for new species to exploit. Once there were plants, animals could come into existence, and the animals themselves sustain large numbers of species of other animals that prey on them, as well as of parasites and symbionts. Thomas Huxley likened the expansion of life to the filling of a barrel. First, the barrel is filled with apples until it overflows; then pebbles are added up to the brim; the space between the apples and the pebbles can be packed with sand; water is finally poured until it overflows (see Huxley and Huxley, 1947). His point is that with diverse kinds of organisms the environment can be filled in more effectively than with only one kind. But Huxley's analogy neglects one important aspect of life, namely that the space available for occupancy by other species is increased rather than decreased by some additions. A more appropriate analogy would have been that of a balloon or an expanding barrel.

It is difficult to estimate the number of individuals living on the earth today with any reasonable approximation, even if we exclude microorganisms. The mean number of individuals per species has been estimated to be around 2×10^8, but some species like *Drosophila willistoni*, the tropical fruit fly with which I worked for several decades, may consist of more than 10^{16} individuals, and there are more than one million insect species (Ayala et al., 1972). The number of individuals of *Euphausia superba*, the small krill eaten by whales, may be greater

than 10^{20}. It seems certain that there are more individual animals and plants living today, and their bulk is greater than it was in the Cambrian. Very likely, they have become greater in recent geological times than they were at most times since the beginning of life. This is more so if we include the large number and enormous bulk of the human population and of all the plants and animals cultivated by humans for their own use. Eluding microorganisms, it is probable that the number of living individuals has increased, on the average, through the evolution of life. About the abundance of microorganisms, there is little that can be said with conviction. On the whole, an increase in the total bulk of living matter is even more likely than an increase in numbers because larger organisms have generally appeared later in time.

It seems likely that the rate of energy flow has increased in the living world faster than the total bulk of matter. One effect of organisms on the world is to retard the dissipation of energy. Green plants do, indeed, store radiant energy from the sun that would otherwise be converted into heat. The influence of animals goes partially in the opposite direction: the living activities of animals dissipate energy, since their catabolism exceeds their anabolism (Lotka, 1945), but they store energy derived from plants that might have otherwise dissipated into heat. Animals provide a new path through which energy can flow and, moreover, their interactions with plants increase the total rate of flow through the system. An analogy can be used to illustrate this outcome. Suppose that a modern highway with three lanes in each direction connects two large cities. The need to accommodate an increase in the rate of travel flow can be accomplished either by addition of more lanes to the highway or by increasing the speed at which the traffic moves on the highway. In terms of the "carrying capacity" of the highway, these two approaches appear, at first sight, to work in opposite directions, but together they increase the total flow of traffic on the highway.

EVOLUTIONARY PROGRESS

I have argued previously that the concept of progress involves an evaluation of better versus worse relative to some standard of reference. Many standards of reference can be chosen according to which it is possible to measure the evolutionary process of the kind I have called "particular," that is, progress that obtains only in certain evolutionary lineages and usually only for a limited span of time. The numerous writers on evolutionary progress have usually proceeded by identifying one or another attribute as the criterion of progress and have then expanded on how progress has occurred in evolution according to the particular standard chosen. These discussions are often enlightening in that they bring about aspects of the evolutionary process that are particularly meaningful from a certain perspective and enhance our understanding of the process. A common deficiency in some of these discussions is the stated or implicit conviction that *the* criterion of progress has been discovered, often accompanied by a lack of awareness that progress is a value-laden concept rather than a strictly scientific one.

I shall now mention some criteria that have been the subjects of thoughtful discussion on evolutionary progress. I will then, by way of illustration, deal in somewhat greater detail with one specific criterion of evolutionary progress: advances in the ability of organisms to obtain and process information about the state of the environment.

Simpson (1949) has examined several criteria according to which evolutionary progress can be recognized in particular sequences. These criteria include dominance, invasion of new environments, replacement, improvement in adaptation, adaptability and possibility of further progress, increased specialization, control over the environment, increased structural complexity, increase in general energy or level of vital processes, and increase in the range and variety of adjustments to the environment. For each of these criteria, Simpson has shown in which evolutionary sequences, and for how long, progress has taken place.

Bernard Rensch (1947) and Julian Huxley (1942, 1953) have examined other lists of characteristics that can be used as standards of particular forms of progress. Ledyard Stebbins (1969) has written a provocative essay proposing a law of "conservation of organization" that accounts for evolutionary progress as a small bias toward increased complexity of organization. Simon Conway Morris (2003) has argued that, under natural selection, progress is a necessary attribute of the evolutionary process, culminating in intelligent humans. I (Ayala, 1974, 1982, 1988) have examined elsewhere in some detail the increase in the ability of organisms to obtain and process information about the environment, as a criterion of progress that is particularly relevant to human evolution; among the differences that mark off humans from all other animals, perhaps the most fundamental is that humans greatly developed the ability to perceive the environment and to react flexibly to it. George Williams (1966) has examined, mostly critically, several criteria of progress. Two brief but incisive discussions of the concept of progress can be found in G.J. Herrick (1956) and Theodosius Dobzhansky (1970). A philosophical study of the concept of progress has been made by T.A. Goudge (1961). Two splendid multi-authored collections with widespread points of view are G.A. Almond, M. Chodorow, and R.H. Pearce, eds., *Progress and Its Discontents* (1982) and M.H. Nitecki, ed., *Evolutionary Progress* (1988). The most extensive learned exploration of the issue of evolutionary progress is Michael Ruse's *Mondad to Man: The Idea of Progress in Evolutionary Biology* (1996). A more concise elaboration,

yet historically informative and conceptually subtle, as well a profound, can be found in Chapter 4 ("Progress," p. 99−127) of Ruse's *The Philosophy of Human Evolution* (2012).

There is no need to examine here all the standards of progress that have been formulated by the authors just mentioned, nor to explore additional criteria. Writings about biological progress have involved much disputation concerning (1) whether the notion of progress belongs in the realm of scientific discourse, (2) what criterion of progress is "best," and (3) whether progress has indeed taken place in the evolution of life.

These controversies can be solved once the notion of progress is clearly established, as I have done earlier. First, the concept of progress involves an evaluation of good versus bad, or of better versus worse. The choice of a standard by which to evaluate organisms or their features is to a certain extent subjective. However, once a standard of progress has been chosen, decisions concerning whether progress has occurred in the living world, and what organisms are more or less progressive, can be made following the usual standards and methods of scientific discourse. Second, there is not standard of progress that is "best" in the abstract or for all purposes. The validity of any one criterion of progress depends on whether the use of that standard leads to meaningful statements concerning the evolution of life. Which standard or standards are preferable depends on the particular context or purpose of the discussion. Third, the distinction between uniform and net progress makes it possible to recognize the occurrence of biological progress even though every member of a sequence or of a group of organisms may not always be more progressive than every previous member of the sequence or than every member of some other group of organisms. Fourth, the distinction between general and particular progress allows one to recognize progress that may have occurred in particular groups of organisms, or during limited periods in the evolution of life, but not in all of them.

PROGRESS AND HUMAN CONSCIOUSNESS

Once one realizes that recognition of progress is only possible after a value judgment has been made as to which will be the standard against which progress is to be measured (and hence, that there is not *a* standard of progress, or one that is best for all purposes) it becomes possible to seek standards of progress that may yield valuable insights into the study of the evolution of life.

I shall now, by way of illustration, discuss progress according to a particular standard of reference: the ability of an organism to obtain and process information about the environment. I can see two reasons that make this criterion of progress especially meaningful (although not, I reiterate, *the* most meaningful, because no criterion exists that is best for all purposes). First, the ability to obtain information about the environment and to react accordingly is an important adaptation because it allows the organism to seek out suitable environments and resources and to avoid unsuitable ones. Second, it is because the ability to perceive the environment, and to integrate, coordinate, and react flexibly to what is perceived, has attained its highest development in mankind. This incomparable advancement is perhaps the most fundamental characteristic that sets apart *Homo sapiens* from all other animals. Symbolic language, complex social organization, control over the environment, the ability to envisage future states and to work toward them, values, and ethics are developments made possible by man's greatly developed capacity to obtain and organize information about the state of the environment. This capacity has ushered in mankind's new mode of adaptation. Whereas other organisms become genetically adapted to their environments, humans create environments to fit their genes. It is thus that mankind has spread over the whole planet in spite of its physiological dependence on a tropical or subtropical climate.

Increased ability to gather and process information about the environment is sometimes expressed as evolution toward "independence from the environment." This latter expression is misleading. No organism can be truly independent of the environment. The evolutionary sequence, fish to amphibian to reptile, allegedly provides an example of evolution toward independence from an aqueous environment. Reptiles, birds, and mammals are indeed free of the need for water as an external living medium, but their lives depend on the conditions of the land. They have not become independent of the environment, but they have rather exchanged dependence of one environment for dependence on another.

The notion of "control over the environment" also has been associated with the ability to gather and use information about the state of the environment. However, true control over the environment occurs to any substantial extend only in the human species. All organisms interact with the environment, but they do not control it. Burrowing a hole in the ground or building a nest in a tree, like the construction of a beehive or a beaver dam, does not represent control over the environment except in a trivial sense. The ability to control the environment started with the australopithecines (or at least, with *Homo habilis* and other early *Homo* species), some of the earliest organisms that may be called human: some were able to produce devices to manipulate the environment in the form of rudimentary pebble and bone tools. The ability to obtain and process information about the conditions of the environment does not provide control over the environment, but rather it enables the organisms to avoid

unsuitable environments and to seek suitable ones. It has developed in many organisms because it is a useful adaptation.

Some selective interaction with the environment occurs in all organisms. The cell membrane of a bacterium permits certain molecules but not others to enter the cell. Selective molecular exchange occurs also in the inorganic world; but this can hardly be called a form of information processing. Certain bacteria when placed on an agar plate move about in zig-zag pattern, which is almost certainly random. The most rudimentary ability to gather and process information about the environment may be found in certain single-celled eukaryotes (=organisms with a true nucleus). A *Paramecium* follows a sinuous path as it swims, ingesting the bacteria that it encounters. Whenever it meets unfavorable conditions, like unsuitable acidity or salinity in the water, the *Paramecium* checks its advance, turns and starts in a new direction. Its reaction is purely negative. The *Paramecium* apparently does not seek its food or a favorable environment, but it simply avoids unsuitable conditions.

Euglena, also a single-cell organism, exhibits a somewhat greater ability to process information about the environment. *Euglena* has a light-sensitive spot by means of which it can orient itself toward the light. *Euglena*'s motions are directional; it not only avoids unsuitable environments, but it actively seeks suitable ones. An amoeba represents further progress in the same direction; it reacts to light by moving away from it, and it also actively pursues food particles.

An increase in the ability to gather and process information about the environment is not a general characteristic of the evolution of life. Progress has occurred in certain evolutionary lines but not in others. Today's bacteria are not more progressive by this criterion than their ancestors of three billion years ago. In many evolutionary sequences, some very limited progress took place in the very early stages, without further progress through the rest of their history. In general, animals are more advanced than plants; vertebrates are more advanced than invertebrates; mammals are more advanced than reptiles, which are more advanced than fish. The most advanced organism by this criterion is doubtless the human species (Darwin, 1871).

The ability to obtain and to process information about the environment has progressed little in the plant kingdom. Plants generally react to light and to gravity. The geotropism is positive in the root, but negative in the stem. Plants also grow toward the light; some plants like the sunflower have parts that follow the course of the sun through its daily cycle. Another tropism in plants is the tendency of roots to grow toward water. The response to gravity, to water, and to light is basically due to differential growth rates; a greater elongation of cells takes place on one side of the root or stem than on the other side. Gradients of light, gravity, or moisture are the clues that guide these tropisms. Some plants react also to tactile stimuli. Tendrils twine around what they touch; *Mimosa* and carnivorous plants like the Venus flytrap (*Dionaea*) have leaves that close upon being touched.

The ability to obtain and process information about the environment is mediated in multicellular animals by the nervous systems. The simplest nervous system occurs in coelenterate hydras, corals, and jellyfishes. Each tentacle of a jellyfish reacts only if it is individually and directly stimulated. There is no coordination of the information gathered by different parts of the animal. Moreover, jellyfishes are unable to learn from experience.

A limited form of coordinated behavior occurs in the echinoderms, such as the starfishes and sea urchins. Whereas coelenterates possess only an undifferentiated nerve net, echinoderms possess a nerve net, a nerve ring, and radial nerve cords. When the appropriate stimulus is encountered, a starfish reacts with direct and unified actions of the whole body.

The most primitive form of a brain occurs in certain organisms like planarian flatworms, which also have numerous sensory cells and eyes without lenses. The information gathered in these sensory cells and organs is processed and coordinated by the central nervous system and the rudimentary brain; a planarian worm is capable of some variability of responses and of some simple learning. That is, the same stimuli will not necessarily always produce the same response.

Planarian flatworms have progressed further than starfishes in the ability to gather and process information about the environment, and the starfishes have progressed further than sea anemones and other coelenterates. But none of these organisms has gone very far by this criterion of progress. The most progressive groups of organisms among the invertebrates are the cephalopods and arthropods, but the vertebrates have progressed much further than any invertebrates.

Among the ancestors of both the arthropods and the vertebrates, there were organisms that, like the sponges, lacked a nervous system. These ancestors evolved through a stage with only a simple network, whereas later stages developed a central nervous system and eventually a rudimentary brain. With further development of the central nervous system and of the brain, the ability to obtain and process information from the outside progressed much further. The arthropods, which include the insects, have complex forms of behavior. Precise visual, chemical, and acoustic signals are obtained and processed by many arthropods, particularly in their search for food and in their selection of mates.

Vertebrates are generally able to obtain and process much more complicated signals and to produce a much greater variety of responses than the arthropods.

The vertebrate brain has an enormous number of associative neurons with an extremely complex arrangement. Among the vertebrates, progress in the ability to deal with environmental information is correlated with increase in the size of the cerebral hemispheres and with the appearance and development of the "neopallium." The neopallium is involved in association and coordination of all kinds of impulses from all receptors and brain centers. The larger brain of vertebrates, compared to that of invertebrates, permits them also to have a large number of neurons involved in information storage or memory. The neopallium appeared first in the reptiles. In the mammals, it has expanded to become the cerebral cortex, which covers most of the cerebral hemispheres. The cerebral cortex in humans is particularly large, compressed over the hemispheres in a complex pattern of folds and turns. When organisms are measured by their ability to process and obtain information about the environment, mankind is, indeed, the most progressive organism on earth.

I would once more reiterate that there is nothing in the evolutionary process that makes the criterion of progress I have just followed best or more objective than others. It may be useful because it illuminates certain features of the evolution of life. Other criteria may help to discern other features of evolution, and thus be worth examining. Particular organisms will appear more of less progressive depending on the standard that is used to evaluate progress. Mankind is not the most progressive species by many criteria. By some standards, humans are among the bottom rungs of the ladder of life, for example, in the ability to synthesize their own biological components from inorganic resources.

It may be properly questioned whether anything is gained by speaking of evolutionary *progress* rather than of evolutionary advancement or of directional change. The term "advancement" also involves an evaluation and would therefore be subject to the same pitfalls as "progress" (although it seems to elicit weaker emotional disclaimers than progress does). "Directional change," however, is not an axiological concept and, thus, it may be treated as other strictly scientific terms (Gould, 1988, 1997).

The notion of progress seems to be irrevocably ingrained among the thinking categories of modern man and, hence, likely to continue being used in biology, particularly in reference to the evolutionary progress. Indeed, Ruse (1996) in his monumental masterpiece, *Monad to Man: The Idea of Progress in Evolutionary Biology*, has argued that the concept of progress pervades all evolutionary writings, from Darwin to the present. I have, therefore, attempted to clarify the concept to demythologize it. I have argued that "progressive" is an evaluative term that demands a subjective commitment to a particular standard of value. Awareness of this makes it possible to speak of progress in evolution without implying the conclusion that humans are the most progressive organisms. As I have suggested, by some biologically meaningful standards of progress, they are not.

CONCLUDING REMARKS

I believe that the concept of progress as I have defined it and the distinctions I have made may also be useful in the fields of cultural anthropology and, more generally, human history (Hoagland and Burhoe, 1962; Almond et al., 1982). It may be the case that much knowledge in these fields is largely value-free, but we can predicate progress of human historical events only by introducing value judgments. However, once this is recognized, it becomes possible to seek criteria of progress that will yield valuable insights in the study of human history.

Claims that progress has occurred in human history need not imply that progress is universal, inevitable, or unlimited. Like biological progress, cultural progress may have occurred in some societies but not others, during certain periods rather than forever, and it may be subject to certain limits rather than able to proceed without bounds. Where and how progress has taken place are matters for investigation, which, once a criterion of progress has been selected, can proceed according to the normal standards of scholarly inquiry.

REFERENCES

Almond, G.A., Chodorow, M., Pearce, R.H. (Eds.), 1982. Progress and Its Discontents. University of California Press, Berkeley.

Ayala, F.J., Powell, J.R., Tracey, M.L., Mourao, C.A., Perez-Salas, S., 1972. Enzyme variability in the *Drosophila willistoni* group. IV. Genic variation in natural populations of *Drosophila willistoni*. Genetics 70, 113–139.

Ayala, F.J., 1969. An evolutionary dilemma: fitness of genotypes versus fitness of populations. Canadian Journal of Genetics and Cytology 11, 439–463.

Ayala, F.J., 1974. The concept of biological progress. In: Ayala, F.J., Dobzhansky, T. (Eds.), Studies in the Philosophy of Biology. University of California Press, Berkeley, pp. 339–355.

Ayala, F.J., 1982. The evolutionary concept of progress. In: Almond, G.A., Chodorow, M., Pearce, R.H. (Eds.), Progress and Its Discontents. University of California Press, Berkeley, pp. 106–124.

Ayala, F.J., 1988. Can "progress" be defined as a biological concept? In: Nitecki, M.H. (Ed.), Evolutionary Progress. University of Chicago Press, Chicago, pp. 75–96.

Ayala, F.J., 2000. The limits of knowledge and the hope for progress. In: Herrmann, R.L. (Ed.), God, Science & Humility. Ten Scientists Consider Humility Theology. Templeton Foundation Press, Philadelphia and London, pp. 131–152.

Broad, C.D., 1925. The Mind and Its Place in Nature. Kegan Paul, London.

Bury, J.B., 1955 [1932]. The Idea of Progress. An Inquiry into Its Growth and Origin. Dover Publications, New York.

Condorcet, M.J.A.N.C., 1956 [1795]. Sketch for a Historical Picture of the Progress of the Human Mind. Noonday Press, New York.

Conway Morris, S., 2003. Life's Solution: Inevitable Humans in a Lonely Universe. Cambridge University Press, Cambridge.

Darwin, C., 1859. On the Origin of Species by Means of Natural Selection. John Murray, London.

Darwin, C.R., 1871. The Descent of Man, and Selection in Relation to Sex. John Murray, London (Also: Appleton and Company, New York, 1971).

Dobzhansky, T., 1970. Genetics of the Evolutionary Process. Columbia University Press, New York and London.

Ginsberg, M., 1944. Moral Progress. Frazer Lecture at the University of Glasgow. Glasgow University Press, Glasgow.

Goudge, T.A., 1961. The Ascent of Life. University of Toronto Press, Toronto.

Gould, S.J., 1988. On replacing the idea of progress with an operational notion of directionality. In: Nitecki, M.H. (Ed.), Evolutionary Progress. University of Chicago Press, Chicago, pp. 319–338.

Gould, S.J., 1997. Full House. The Spread of Excellence From Plato to Darwin. Harmony, New York.

Haeckel, E., 1896. The Evolution of Man, vols. 2 (Appleton, New York).

Hegel, G.W.F., 1970 [1817]. Philosophy of Nature. Oxford University Press, Oxford.

Herrick, G.J., 1956. The Evolution of Human Nature. The University of Texas Press, Austin.

Hoagland, H., Burhoe, R.W. (Eds.), 1962. Evolution and Man's Progress. Columbia University Press, New York.

Huxley, T.H., Huxley, J.S., 1947. Touchstone for Ethics. Harper, New York.

Huxley, J.S., 1942. Evolution, the Modern Synthesis. Harper, New York.

Huxley, J.S., 1953. Evolution in Action. Harper, New York.

Kimura, M., 1961. Natural selection as the process of accumulating genetic information in adaptive evolution. Genetical Research 2, 127–140.

Lamarck, J.-B., 1809. Philosophie Zoologique. Duminil-Lesueur, Paris (English Translation: Elliot, H. 1914. The Zoological Philosophy. Macmillan, London.).

Leroi, A.M., 2014. The Lagoon. How Aristotle Invented Science. Viking, New York.

Lewontin, R.C., 1968. The concept of evolution. In: Sills, D.L. (Ed.), International Encyclopedia of the Social Sciences, vol. 5. Macmillan Co. and Free Press, London and New York.

Lotka, A.J., 1945. The law of evolution as a maximal principle. Human Biology 17, 167–194.

Lovejoy, A.O., 1960 [1936]. The Great Chain of Being. A Study in the History of an Idea. Harvard University Press, Cambridge, MA.

Nitecki, M.H., 1988. Evolutionary Progress. University of Chicago Press, Chicago.

Rensch, B., 1947. Evolution above the Species Level. Columbia University Press, New York.

Richards, R.J., 1988. The moral foundations of the idea of evolutionary progress: Darwin, Spencer, and the Neo-Darwinians. In: Nitecki, M.H. (Ed.), Evolutionary Progress. University of Chicago Press, Chicago, pp. 129–148.

Ruse, M., 1996. Monad to Man. The Idea of Progress in Evolutionary Biology. Harvard University Press, Cambridge, MA.

Ruse, M., 2012. The Philosophy of Human Evolution. Cambridge University Press, New York.

Simpson, G.G., 1949. The Meaning of Evolution. Yale University Press, New Haven.

Simpson, G.G., 1953. The Major Features of Evolution. Columbia University Press, New York.

Smith, A., 1937 [1776]. The Wealth of Nations. Modern Library, New York.

Spencer, H., 1852. Progress: its law and cause. Westminster Review 67, 244–267. Reprinted in 1868. Essays: Scientific, Political and Speculative. Williams and Norgate, London, vol. 1, pp. 1–67.

Spencer, H, 1862. First Principles. Williams and Norgate, London.

Stebbins, G.L., 1969. The Basis of Progressive Evolution. University of North Carolina Press, Chapel Hill.

Thoday, J.M., 1953. Components of fitness. Symposia of the Society for the Study of Experimental Biology 7 (Evolution), 96–113.

Thoday, J.M., 1958. Natural Selection and biological progress. In: Barnet, S.A. (Ed.), A Century of Darwin. Allen and Unwin, London.

Thoday, J.M., 1970. Genotype versus population fitness. Canadian Journal of Genetics and Cytology 12, 674–675.

Williams, G.C., 1966. Adaptation and Natural Selection. Princeton University Press, Princeton.

Chapter 34

Culture, Brain, and Behavior: The Implications of Neural Plasticity and Development on Social Contexts and Political Structures

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The human mind and brain display remarkable plasticity and develop in a particularly social context within larger cultural environments. In this way, the human mind, and human nature, evolve in constant interactive interaction with larger social and cultural processes. Neither the genetic and biological processes, nor cultural institutions, are fixed or static; rather, they each reciprocally shape and inform each other in rich, ongoing, and dynamic ways. This chapter seeks to examine some of the recent work that has been done at the intersection of these forces, and hopefully enlighten how a more comprehensive understanding of these processes can shed light on producing a more optimal convergence between nature and nurture for the benefit of those most vulnerable to misalignment between these processes.

This chapter is organized around four central themes related to this broader topic. Clear overlap exists between these issues, and the distinctions between them often appear artificial or imposed. Other forms of organization are certainly equally legitimate. However, for purposes of investigation, these topics serve as focal points of inquiry. The first section explores which aspects of brain function are likely to be most susceptible to cultural conditioning, and which might prove most resistant. The second part examines the interaction between genetic predispositions and various motivational drives, examining how various environmental inputs can help reconstitute, shape, and otherwise inform basic biological processes. The third question investigates the reverse process, inquiring into the ways cultural practices can affect gene expression, epigenetic processes, through development and other environmental inputs. Finally, special attention will be given to the interaction of cultural and developmental processes across levels of analysis. Because of the pressing and pervasive nature of this concern, most of the specific applications, implications, and ramifications of this discussion throughout are focused on the emergence and nature of mental illness.

THE INTERACTION OF BRAIN AND CULTURE

Any successful evolutionary process must allow for inputs from the environment to signal important repeated challenges and opportunities to an organism. For this reason, we would expect the human brain to be attentive to such information, especially over the course of early development, precisely because such cues provide critical input about the kind of environment that the individual will encounter, whether it be characterized by abundance or deprivation, support or abuse. These environmental inputs help trigger the expression or suppression of particular genetic capacities; and while each individual may possess remarkable plasticity, hard boundaries around particular capacities will exist. Take height as an example: good nutrition and care will allow a person to maximize their potential, but there will be an absolute genetic limit to how tall a given individual can grow to be, even under the best

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00034-X

of circumstances. However, it is worth inquiring into which mental processes we would expect to be most heavily influenced by various environmental factors, such as nutrition in the example just provided, and which would we expect to remain more universal in manifestation, or more likely moved to fixation and thus relatively impervious to cultural variation across time and space.

This section examines this question in three specific ways. First, an overview of the interaction between brain, culture, and behavior is provided, with an eye to the most pressing questions and problems confronting our understanding of this area of inquiry. Second, various approaches to the way in which culture might shape brain structures is discussed. Finally, the implications and application of this approach for mental health research and treatment are described.

Culture, Mind, and Behavior

In his popular book, *The Better Angels of our Nature*, Steven Pinker (2011) argues that we are living in possibly the most peaceful time in our history. He documents the decline in violence over the course of human history, and he delves into some of the evolutionary reasons for why and how this transformation has taken place. In so doing, he posits deep psychological mechanisms that he argues constitute innate, universal aspects of human nature. And although this is not his central question or concern, he leaves open the exact structure and function of these deep mechanisms. Yet, clearly if outcomes have changed over time, and have been influenced by large-scale social revolutions such as the Enlightenment, as he argues, then these innate aspects of human nature clearly interact with environmental, social, and cultural variables to produce this valuable and important decline in human violence over time. So how are we to think about the interaction of these human universals with cultural factors, whether on a large-scale like the Enlightenment, or the domestication of animals and the growth of agriculture, or on a smaller scale, including the birth of political and economic institutions?

Experience is patterned by culture, and, as a result, the mind may be shaped by various cultural variables to a greater extent than we imagine. This culturally patterned behavior and experience can, in turn, literally influence patterns of connectivity within the brain. We know, for example, that something as seemingly simple and ordinarily as learning to play chess or the piano can, in fact, influence, shape, and change patterns of brain connectivity in just this way. And if learning a game or a musical instrument can accomplish such a task, imagine what learning a set of complex religious beliefs or political principles might entail. Indeed, in this way, the brain may be a crucial site for the accumulation of cultural information over a relatively long span of time. It literally houses our cultural history within our skull.

But before exploring this topic further, it might be useful to first clarify our definitions. There are, for example, many different meanings of culture. What do I mean by the use of the term? When I refer to culture, I intend to encompass the meaning, values, and lay theories and practices, or scripts, which unite, and may even govern, a group of people that adhere to them. This typically includes at least three critical elements: (1) values, or the general goals or personal states that are endorsed by a given culture; (2) practices, or those scripts and behavioral routines that are designed to achieve those culturally endorsed goal states; and (3) psychological tendencies, which sustain active participation in those cultural tasks.

A model that incorporates cultural into the evolution of the brain might be referred to as a neuro-cultural interaction model, where the brain is understood as a crucial site that accumulates cultural information (Kitayama and Uskul, 2011). In this way, the process involved in incorporating culture into psychological mechanisms becomes fundamentally behavioral rather than merely cognitive in nature.

What would be required for such a deep interaction to take place over time in such a way that these psychological mechanisms can become instantiated in genetic structure? A few factors must necessarily be logically involved. First, the cultural features themselves likely take place at a macro level, but could involve large-scale economic, political, ecological, and societal factors. Climate change or large-scale social mobility from drought, famine, or natural disasters might also qualify in this realm, especially if they help precipitate population change through in-migration, genetic drift, recombination, assortative mating, or other ecological conditions. In addition, a society's cultural values, tasks, and practices are developed and designed to achieve consensually agreed upon cultural values. People in that culture then repeatedly engage in a select set of cultural tasks, depending on what a given situation or environment may call for at a particular time and place. These practices may then lead to long-term changes in collective patterns of neural activity that facilitate the perpetuation of these cultural practices. These now psychologically instantiated patterns of connectivity can reproduce the spontaneous enactment or reenactment of culturally scripted behaviors when such behaviors are called for given particular environmental opportunities or constraints. The manifestation of these practices thus helps establish individual identity within the group, and it establishes a person's reputation as a member of a particular coalitional community. This advertising and acknowledgement of coalitional status is key not only to cultural continuity, but also to the benefits that derive from such membership, including cooperative ventures and mating opportunities. Without such community ties, individuals as social animals are less likely to

survive in the face of harsh environmental conditions and predation. In turn, the biological adaptivity of a given set of cultural practices then can be evaluated by their relative reproductive success.

In this way, the feedback loop that influences reproduction, as well as prosperity through cooperative ventures, can change cultural practices and identity formation and enculturation over time. This can result in neuroplastic changes in the brain itself, as both an affirmation of self-identity and coalitional status, but also to enhance individual well-being. Biological changes can result across generations as various aspects of cultural practice either enhance or inhibit the probability of survival and reproduction.

Good evidence in support of this argument comes from studies of differences between individuals from cultures traditionally depicted as valuing independence, such as Western culture, and those differentially valuing interdependence, such as eastern cultures. These are understood to represent foundational values and provide the wellspring source for many practices within each respective culture. In a functional imaging study, Zhu et al. (2007) found that culture affected the functional neuroanatomy of people from different cultures in the domain of self-representation. They showed that Western subjects showed differential brain activation patterns for judgments about the self and mother, while Chinese used the same structures to think about self and mother, showing that culture values around individuation resulted in notable differences in patterns of brain activation.

How might these different processes emerge? Such practices clearly involve both an element of choice as well as culture influence. Over time, people imbued in an independent culture come to invest themselves in choices that are made largely in private, whether as a result of intrinsic motivation or cognitive dissonance, whereas those who grow up in an interdependent culture differentially invest themselves in choices made in public, choices which need to be publically anchored before they can exert an impact on motivation, and thus have impact on the self. These patterns may develop early, and be moderated by reinforcement through very subtle social cues, such as eye gaze from caretakers, and surveillance regarding when children are watched or not watched based on what they are doing. In this way, brain response can be modulated by social cues in the eyes; such cultural practices can thus automatically replicate themselves as they become deeply ingrained at an unconscious level, yet predicted by patterns of social reinforcement. These patterns may differ by domain, and self-representation represents only one potential area, but social and socio-emotional relations are likely imprinted in this way early on, and thus may be less malleable to environmental change over time as an individual reaches adulthood. In this way, culture becomes embedded into evolution by helping individuals achieve biological imperatives such as early social support, attachment that facilitates mating, and parental bonding that optimizes child-rearing. Thus, cultural acquisition becomes a critical way in which people prepare themselves for the reproductive market.

Culture and Brain Structure

The brain may be the proximal cause of any given behavior, but culture still exerts a durable influence on behavior as well. And as just noted, social identity can cause durable changes in the brain as well. Han et al. (2013) discuss just these phenomena in their cultural neuroscience approach to the biosocial nature of the human brain. Building on an earlier definition she had put forth with Chiao and Ambady (2007), Chiao (2010, p. 109) defined cultural neuroscience as an "interdisciplinary field bridging cultural psychology, neurosciences and neuro-genetics that explains how the neurobiological processes, such as genetic expression and brain function, give rise to cultural values, practices and beliefs as well as how culture shapes neurobiological processes across macro- and micro-time scales." And increasing evidence has been demonstrating the various ways in which cultural background and upbringing influence neural substrates in differential ways, at both high and lower levels of cognition (Han and Northoff, 2008; Worthman et al., 2010).

There are at least two domains in which culture can be represented in the brain, and it can exert different properties in each (Richerson and Boyd, 2008). First, culture can help organize brain structures, through a long history of coevolution between the human brain and social structures. Indeed, there are large brain areas that have adapted to taking on cultural components, including learning intrinsically motivated domains such as language acquisition, social organization, and the use of technology such as tools. Second, culture can reorganize brain structures that may have evolved for different purposes. After all, the brain is highly plastic, and even over a shorter history of ostensible coevolution with cultural practices, various aspects of brain function have been recast for new but related purposes. For example, learning that requires extrinsic motivation may have emerged in several domains, including reading and writing as by-products of language, and more complex forms of social organization, as may occur in egalitarian states.

Gene-cultural coevolution will tend to convert and reorganize brain structures into more organized ones through processes of exaptation. Coevolution between genes, brains, and culture represents an ongoing process (Richerson and Boyd, 2008; Cochran and Harpending, 2009; Chiao, 2009) with continual reciprocal iteration. Autism can be seen as a model for representing what

coevolution has accomplished because treatment requires teaching a set of social rules that appear automatically and occur spontaneously in those who are unaffected.

Nevertheless, although culture remains highly complex and variable, its transmission must remain based on efficient mechanisms of social learning. This can take place through various mechanisms, such as processes of imitation (Tomasello et al., 1993; Tomasello, 1993), including biased imitation and joint attention (Carpenter and Tomasello, 1995; Tomasello, 1999) and social learning (Nagell et al., 1993). One of the most interesting and productive methods of investigating the acquisition of culture has involved the comparison between monkeys and young human children in various aspects of social learning (Drayton and Santos, 2014; Leimgruber et al., 2014; Rosatiet al., 2014). This work illustrates not only the evolutionary bases of some forms of social learning in humans, but it also points to important discrepancies between what monkeys do and what humans do. In some cases, young children's tendency to imitate can make them less efficient than monkeys in various problem solving tasks. Whiten et al. (1996) examined contrasts between chimpanzees and humans in observational learning. McElreath et al. (2008), using both an evolutionary model as well as experimental tests, demonstrate the individuals employ both payoff information as well as information about frequency in making their strategic decisions about which social information to utilize. Using an fMRI study, Vogt et al. (2007) demonstrated that various aspects of the dorsolateral prefrontal cortex were involved in selecting and integrating existing functions within the mirror neuron system in processes of imitation. Keysers and Gazzola (2010, 2014) provide additional evidence implicating the role of mirror neurons in facilitating processes of social learning, including the ability to engage in joint action, and utilize projection to enhance mind reading capacity. Bloom (2002) argues that this mind reading ability allows for word learning as one aspect of a broader inferential mechanism that also potentiates the ability to represent others' mental states. In another magnetic resonance imaging (MRI) study, Dehaene et al. (2010) show that literacy, attained either in childhood or adulthood, literally changes cortical organization, providing profound evidence that culture can change the structure, as well as the function of human nature. Of course, this work acknowledges that large individual differences exist, including dysfunctions such as dyslexia, as well as differences in learning to read and write, or connect the object recognition system to the referential language system. Marinkovic et al. (2003) explored the relationship between these auditory and visual systems in trying to map the representation of object recognition. They found that these systems really take place in different parts of the brain but come together in the language center. Anderson (2010) posits that neural reuse models can help explain how brain circuits that evolved for one use can be exploited and redeployed for other uses to help explain how such processes of cortical reorganization could take place, suggesting some application not only for understanding the effect of literacy on cortical reorganization, but also other cultural acquisition processes such as tool use.

This critical work outlines very specific aspects of cultural learning, and how they take place within the human brain. But if we broaden out to return to Pinker's larger point, which instigated this section, regarding what is deeply universal in human nature, many take this point to imply an almost unalterable nature of human mind. Yet the human mind remains a product of evolution, and this understanding requires a shared assumption that the human mind is alterable over time, in constant interaction with environmental variables. So, how do we define flexibility and malleability of the mind? And what kind of time line would this require? Even more to the current point, can sociocultural influences reorganize the very mechanisms by which we learn culture itself? Can, or should, we learn how to transmit culture differently?

One of the interesting points in this regard relates to how social support can affect the interaction between genes and culture. If we learn culture in part through the ways that we imitate and interact with others, then the degree and kind of social support involved in these processes becomes critical. Yet, there is some evidence that cultural differences exist in social support seeking, with emotional social support seeking being more normative in Western cultures like the United States than in other cultures in East Asia, in particular, indicating that variance, rather than universality, may drive at least some aspects of cultural adoption and transmission. Luo and Han (2014), Luo et al. (2015), and Han and Ma (2015) found that the expression of a polymorphism on the oxytocin receptor (rs53576) predicted processes of both social support seeking and emotion regulation. Those Americans with the AA type used more emotional suppression than those with the GG type, although the opposite pattern was found among Koreans. Similarly, Americans with the GG type sought more emotional social support than those with the AA type, but only under conditions of distress; Koreans did not display any such differences in social support seeking by genotype. Such differences suggest not only that behavioral phenotypes may differ across cultures, but that culture itself can moderate behavioral outcomes associated with particular genotypes. This suggests that when a person experiences a basic need or psychological tendency, it can be expressed differently depending on culture because that disposition responds to the environment differently depending on where we are and what kind of social and ecological reinforcement we receive for the expression or suppression of various behaviors.

Culture–gene coevolution thus demonstrates one way in which behavior can affect both brain structure and function. But what is the point of studying the brain if we already know a person's behavior? Precisely because the brain can indicate more proximate mechanisms about how cultural information comes to be stored in the mind, the brain serves as a physical repository of cultural information and provides information about how culture and mind interact to produce the behavior we witness.

If brain activity is mediated by social context, then MRI studies may be able to provide some information about some of the ways in which such processes take place, especially by comparing before and after images occurring across some intervention. However, such inferences may provide only weak evidence, since the inferred region of putative operation in the brain can make a huge difference in the interpretation of subsequent data received. Depending on the question of interest, other methods may prove more useful. Such approaches might include genome-wide association studies; however, genetic effects often exist at very small sizes, often only in interaction, and thus require population samples in the thousands, which can limit some kinds of investigations due to financial or logistical limitations. Pooling across consortiums might allow for the incorporation of greater ethnic diversity in samples, while in-depth profiling and phenotyping of a more limited number of individuals may allow for an investigation of more novel genetic contributors, rendering trade-offs in both time and money inevitable in these kind of investigations.

What do we learn by adding brain phenotyping into an equation designed to understand the sources of human nature? Is such categorization better than other kinds of behavioral measures? Brain phenotyping can provide a certain level of information that would be hard to get from behavior alone, and it can help make predictions about what various brain regions tell us. We can then use that information as a signature that allows us to examine related processes in that region. By obtaining more information on pathways of brain connectivity and location with regard to particular processes, or behavioral outcomes, we can better understand the psychological mechanisms that entrain various kinds of behavior.

These processes are neither simple nor reductionist. It is not that genes cause behavior directly, or that culture affects genes directly, because more is involved than a simple mapping across levels of analysis, but examining the relationship between genes, culture, and behavioral outcomes of interest can allow us to begin to try to illuminate the ways that genes worm their way up in influence, just as culture drills down its influence simultaneously. Complex behaviors are likely produced by different mechanisms involving multiple systems across various levels of organization; the level of complexity is geometric, not arithmetic in nature. Observers are inevitably reductionist when making attributions about other people's areas. But if we want to learn more about the biological substrates of behavior, and how these factors might facilitate or limit human expression and experience, we need to mix levels of analysis in examining outcomes of interest. The challenge is not to confound explanations across various levels of analysis. And the question is how to do this without becoming too reductionist, or too mired in the political implications and associations of reductionism. This is important because studying the distribution of various genetic factors across a population, or between populations, can be meaningful for investigating where and how common variance may be adaptive and useful in one context, moot in a second, and perhaps dysfunctional in a third.

Culture and the Human Brain

If there are functional as well as anatomical changes in the brain as a function of cultural experience, as the aforementioned work suggests, then what are the critical developmental periods for cultural influence on such changes? One of the challenges in exploring this question relates to the paucity of longitudinal brain imaging work, which makes it difficult to track the evolution of these processes over developmental time.

However, some things are known. It has been well established that neural plasticity is a common experience of the brain (Hubel and Weisel, 1962; Hirsch and Spinelli, 1970). In addition, training, as well as experience, affects the anatomical structure of the brain. In a famous study of jugglers, Draganski et al. (2004) showed context-dependent learning produced not just functional but anatomical changes in the brain by demonstrating changes in the part of the brain associated with processing complex visual motion. Thus, experience modulates brain structure and anatomy. As a result, it becomes possible to conceptualize culture as an experience that influences the brain in prolonged and profound ways. Thus, we would expect to see a strong influence of culture on the brain. However, it is possible that different cultural systems affect which domains would benefit from conserving plasticity and which might be better served by moving to fixation or extinguishing altogether. Features present in the early environment may help inform such practices at an individual level, but these experiences would not necessarily expand or generalize into larger cultural changes, although it is certainly possible that larger cultural changes are instigated in part by such shifts, particularly if they occur among multiple members around the same time. One can imagine that greater tolerance for diverse sexual practices might have emerged in this fashion.

If we expect this, where would be expect to see it? How would we expect to observe such effects? And what do we

mean by culture? Is it malleable? How do we divide it into meaningful sections for investigation independent of the brain that processes and reproduces it? Is the brain the seat of all thought, feeling, and action? Should we pay more attention to what is going on inside the head than what is going on in the world around us? Or should more attention and effort be focused on theorizing about the nature of context and culture independent of brain science?

Importantly, cultural values themselves help shape our interpretation of research on the brain and culture (Markus and Kitayama, 2010). Specifically, we exist and work at a watershed cultural moment that has produced a different and shared notion of what it is to be a person. Western culture and civilization has built one model of a person, and we live within the historical legacy of that notion. This idea, going back at least to Descartes (1637), constructs an autonomous bounded image of an individual as a thinker; this notion has infused our science, so that when we think of a person we think of a thinker, a disembodied person who exists separate from their environment, work, and cultural context. He operates separately from others, thinking, not doing, moving, feeling, or engaging. This notion has established our traditional and historical legacy and grounds the assumptions that scientists have largely worked with across many generations. But this vision has morphed dramatically. Now, science shares the view that the unit of analysis needs to be a person (brain) in constant interaction with his or her environment, and it recognizes the needs to study that entire cycle in an ongoing and reciprocal way. We now understand that a person and his or her brain is shaped, conditioned, and changed by many aspects of the environmental context, including other people, and in turn, it continually evolves and shapes those structures, environments, and others as well. As a result, our unit of analysis is shifting, and our interpretations have begun to change as well, as we come to recognize the malleable nature of the person and how each individual depends on, and needs, their environment to be complete. Yet, this view of humans as interdependent, social, relational, malleable individuals who engage in constant neuronal recycling to recruit and reuse biological structures in a dynamic cycle between genes and environments does not yet represent the popular press, or even the informed public's notion of human nature.

So, this makes it difficult to think about how best to examine and interpret the meaning and function of the aforementioned neural plasticity in a broader cultural context. The brain can display large-scale changes in connectivity as a result of training and experience, as mentioned earlier, but that need not imply local functional differences. However, such local changes can nonetheless result in larger change as well. In particular, there are at least two different kinds of connectivity: physical, which can sometimes be detected using MRI technology, and functional, which can be examined using diffuser tensor imaging, which cannot give physical connectivity information. There should be detectable differences in connectivity, but this may not necessarily indicate whether or not these differences are real or true. Is physical connectivity correlated with cultural difference? Can you manipulate functional connectivity? What areas co-vary or coactivate? What regions of the brain cooperate under different circumstances (for example, resting versus task specific)? If culture makes a difference, does it make a difference to resting state? If so, that would suggest that culture can induce a global change in connectivity, not simply transient, task-dependent changes. If it does make a difference in task connectivity based on embedded culture, how might this change over time, and what might be the underlying mechanisms for such change over time?

Clearly neuro-genesis is not restricted to children, but it occurs in adults as well, demonstrated perhaps most famously in the study of hippocampi in taxi drivers in London, whose representations of spatial size increased as a function of their job (Maguire et al., 2006). This study showed that particular environments can cause changes in certain areas of the brain. In addition, various developmental phases certainly precipitate profound changes, including puberty, pregnancy, or menopause, and age alone affects both the brain and the experience of culture. Sex hormones prove critical in puberty, producing secondary features and synaptic pruning. Paus et al. (1999) show increases in white matter in the brain during adolescence, and gradual maturation that supports speech and motor functions. So, clearly, the brain is adapted for variation and flexibility both in biology and in interaction with local ecology, and these facets enlighten our understanding of how people acquire and enact culture.

Culture shapes how we want to feel and how we define health and illness. In particular, culture shapes what we think of as normal, thus influencing how clinicians assess, treat, and define mental health and mental illness. After all, culture shapes illness, how we define it, and how it is expressed. Disorder manifests differently across cultures, and there is rarely, if ever, a single biological marker for a particular mental illness (Jansma et al., 2004; Zhang and Raichle, 2010). In short, culture defines the disease, not simply affecting its expression. Thus, clinicians need to think about how a particular mental illness is situated within the larger culture context and how particular illnesses some to be defined by culture because the same illness can play out differently across different cultures: what looks odd in an American context will differ from an Asian one. And even within certain cultures, differences can emerge; behavior that looks normal in one subgroup can appear quite extreme in another, as can be seen in comparing Amish to normal American subcultures, for example. And huge individual variance can exist even

within specific cultural contexts. But, regardless, culture affects the assessment, definition, and treatment of mental illness, and treatment itself varies within particular cultural contexts. Clinical assessments need to take culture into account in assessing illness if they are to be comprehensive and accurate.

Yet, we know almost nothing about the intergenerational transfer of notions of ideal emotional experience and expression across immigrant population and how that affects parent–child communication. But it is certainly possible, if not likely, that such interactions might switch the circuitry of underlying behavior depending on cultural context and patterns of parental interaction. And certainly methodological challenges are presented by history and experience that can be transgenerational in nature. Rather, we often use highly nonrepresentative samples to make our characterizations of human nature in what has become known as the science of WIERDs (white, industrialized, educated, rich, and democratic). Whether this sample represents the broader cultural group we are trying to understand remains an open question.

GENETIC PREDISPOSITIONS AND MOTIVATIONAL DRIVES

One of the first questions that needs to be addressed in examining the interaction between genetics and culture revolves around whether or not evidence exists that positive selection has occurred around particular functions or behaviors. Wang et al. (2006), using a 1.6 million single nucleotide protein (SNP) genotype data set, found evidence for such positive selection using an innovative linkage disequilibrium decay technique to demonstrate such selection in 1.6% of SNPs. Replicating these findings with an independently generated sample of one million SNPs, they locate evidence for genetic selection in areas such as host–pathogen interactions, reproduction, DNA and protein metabolism, and neural function. None of these areas should be surprising, since all these dynamics would have presented repeated challenges that humans would have needed to overcome across time and space to survive and flourish.

Successful mechanisms and strategies would be expected to reach fixation and achieve uniformity over time, except for a few mutations as a result of normal transient injuries and in-migrations. The question then becomes whether such genetic instantiations can become highly geographically differentiated. Big differences in vital areas such as vision or metabolism would not be expected to occur often or randomly, because such difference should not occur by chance, but rather as a result of positive selection on the basis of ecological variability, as might be expected to occur in skin pigmentation based on degree of sun exposure.

For evidence of a more universal effect of positive natural selection on significant behavioral traits, we would look for similar effects in different places. Of course the interaction of genetics and culture represent subtle, iterative, and interacting processes, and recent evidence suggests that the rate of human evolution has been accelerating over time, at least partly as a function of increased population; changes in culture and ecology affect human demographic growth, and vice versa (Hawks et al., 2007). Cochran and Harpending (2009) argue that these changes have become exponential over the last 10,000 years as humans have changed their environments and thus radically changed their ecology as well. Specifically, they examine how changes such as increased lactose tolerance and disease resistance allowed Europeans to formulate a new way of life. In particular, such forces as the domestication of livestock and the development of agriculture intertwine with human biology to spur more rapid genetic changes over time.

Of course, mutations in genes do not always serve to improve the ability of humans to survive, but such mutations are, by definition, unlikely to survive across many generations. According to Rogers and Harpending (1992), the number of mutations that appear in a population respond to selection pressures as a linear function of the number of people in that population, so as the population grows, it accelerates the number of possible new mutations, creating opportunities to respond to selection pressures that are not present in the context of smaller populations. With environmental change, most new mutations do not survive. It is, after all, easy for mutations to damage things, and much rarer to witness mutations making things better for humans, on average. As a result, most new mutations do not survive, although sometimes there can be an advantage to a decrease in some genes, or an advantage to heterozygosity, as when extreme selection pressures can produce such outcomes with diseases such as sickle cell anemia or thalassemia in response to the threat of malaria, or cystic fibrosis protecting against typhoid fever. In other words, some mutations that help you reproduce faster in some geographic areas do not necessarily help you survive in other environments. In this way, evolution can give with one hand and take away with another.

Cultural Neuroscience: Culture–Gene Interactions on Brain and Behavior

The preceding discussion raises an important question. If environment can influence biology, then what aspects of the environment matter? Many aspects of an environment or culture could potentially exert an influence on human biology in an influential and reciprocal manner. Potentially anything from living in an urban versus a rural environment to variants in religious beliefs and practices could affect

human behavior in decisive ways that could affect biology. Indeed, human virtues that designate good or bad, beautiful or ugly, also help create practices that help formulate critical aspects of social and ecological environments. What do we know about culture, and how it might integrate with environments in meaningful ways? How does culture influence our neurological representations of the self? How do we map cultural values to neural processes, using some combination of culturally appropriate surveys and advanced neuroimaging or genetic studies (Chiao, 2009)? How might we examine how fluctuations in neural functioning might be shaped, affected, or otherwise modulated by cultural values (Chiao, 2010)?

Many of our scientific models remain constrained by our samples, and prevent us from being able to fully delve into the ways that internal versus external representations and maps of the world, or the mapping of physical environment or mental states to biological ones help shape, instigate, and sustain dynamic culture–biology interactions. The recognition of the simultaneous temporal and spatial interactions in development have led to increased focus on the way neuroplasticity allows for the interplay of culture and biology in shaping brain and behavior across the entire lifespan (Li, 2003).

Such diversity in the shaping of brain and culture obviously offers some important benefits, but it simultaneously places demands on an individual to try to achieve understanding and communication across the inevitable gulf in human experiential reality, thus placing a premium on the need for empathic processes to overcome such challenges (Hein and Singer, 2008).

Diversity represents a kind of adaptation to allow for humans to survive and thrive across a wide variety of ecological and social contexts across time and space that takes place across multiple levels of analysis (Chiao and Ambady, 2007; Chiao, 2009). Such flexibility in human development helps potentiate the culture–gene coevolution processes that help shape brain, behavior, and culture, and allow them to vary in ways that may prove differentially beneficial. For example, Chen et al. (1999) showed that different populations differed in their propensity to carry the long variant of the dopamine D4 receptor (DRD4), which has been associated with novelty seeking. They seek to tie this variance to propensity for migration among nomadic versus sedentary populations. Variants on this receptor (DRD4/7R) may have provided advantages to nomadic populations by affecting body mass index, which could prove critical to survival in chronically undernourished populations, such as nomadic tribes (Eisenberg et al., 2008). If certain people who are then predisposed toward such novelty seeking were then placed in sedentary jobs, the risk for what then becomes labeled hyperactivity and obesity becomes obvious, although the advantage of that predisposition in the context of a different set of environmental pressures also remains clear. Similarly, Green et al. (2008) found a relationship between variants in COM-T and egalitarian versus despotic tendencies not dissimilar from that found in primates. Such variance could provide insight into who leads and who follows in-migration patterns, among other outcomes related to leadership patterns. In this way, it becomes possible to see how mapping cultural to genetic features can help inform the evolution of human behavior in the context of gene–environment interplay.

One of the constant pressures most likely to have shaped various aspects of culture–gene coevolution would relate to pathogens and the need to avoid contamination and infection, and this would have always varied by location, as indeed it does now. Some areas are more susceptible to certain kinds of pathogens than others because of temperature, local pests, and other factors. Fincher et al. (2008) tested the notion that cross-cultural differences in important human behaviors differ by the rate of pathogens in local environments by examining cultural variation in individual versus collectivist values. They suggest that cultural values privileging collectivism would enforce practices such as ethnocentrism and conformity that would have reduced the likelihood of transmission of pathogens, and therefore they would be expected to be more prevalent in areas that historically had experienced higher rates of pathogens. And indeed, controlling for other factors, they find this to be the case. Similarly, Fincher and Thornhill (2008) make a similar argument to account for greater religious diversity in areas with higher pathogen rates. They suggest that areas with dense pathogens select for behaviors that encourage in-group sociality, outgroup avoidance, and limited interaction across groups. Because such isolation and strict boundaries lead to more groups being established, those areas with more pathogens should foster a greater diversity in cultural practices such as religion, and indeed this is what they find in both traditional and modern cultures.

In important extension of this argument to the realm of mental health, Chaio and Blizinsky (2009) found a relationship between genetic variance on the serotonin transporter gene (5HTTLPR) and cultural values along the individualist–collectivist cultural continuum examined by Fincher et al. (2008) with regard to pathogens. They found that collectivist cultures were more likely to possess the short form of the allele, which as with Fincher et al. (2008) can be predicted by the historical prevalence of pathogens. Interestingly, those who carried the short form of the allele showed lower rates of mood disorders in the context of collectivist cultures, suggesting that culture can provide a buffering effect for those who might otherwise be at increased risk for such disorders. This is consistent with findings reported by Canli and Lesch (2007), who reported a relationship between genetic variants on this transporter gene and processes involved in emotion regulation and

social cognition, showing how life stress can modify its functioning in the brain. Culture would certainly serve to either exacerbate or ameliorate the role of life stress in the functioning of all kinds of activities in the brain.

This work demonstrates that the short allele on the serotonin transporter shows greater prevalence in east Asian regions where disease and pathogens were more prevalent historically, and this variant of the allele appears to work to protect the population from mood disorders in the context of collectivist cultures. But this social regulation may work too well in other contexts, causing adjustment problems when it appears within the context of more individualist cultures. Importantly, the parent–infant remains a relationship exceedingly important in determining the impact of this allele in humans and monkeys: with bad parenting, the short allele leads to risk, but with good parenting, it leads to adaptive outcomes. The allele works to affect an individual's sensitivity to culture; and parenting style is passed intergenerationally by nongenetic factors as well as genetic factors. A person can have the short version of the allele and be good parent. But most people parent according to the kind of parenting they experience, causing increased risk in children that are exposed to both genetic and nongenetic risk factors in terms of mood disorders.

Studies that attempt to relate cultural traits to genetic influences can be very challenging to pursue. It can be very difficult to identify associations between cultural factors and genetic traits, both within much less across populations. Using information from genome-wide association tests both within and across populations, it would be important to identify how culture interacts with identity and other aspects of brain function to inform the delicate and sophisticated reciprocal interaction between brains, culture, and behavior. Nonetheless, as these studies demonstrate, cultural values can shape neural representations, and neural processes can systematically differ as a function of cultural values and forces.

Research Implications

Examining the effect of the various phenomena raised earlier is not always easy or straightforward. The effects of environment and experience are not at all the same; the latter is more personalized. Stimuli does not always map well to experience, and how environmental factors as opposed experiential ones are measured will likely differ. And, to complicate things further, neural plasticity in the brain can shift as a result of both developmental factors and vary with social and cultural context, including in the ways described earlier.

Exposure to various aspects of the environment does not happen randomly either. Individuals select into different environments, friendship networks, and experiences. And while culture and such factors as ethnicity can affect these selections, so can genetic factors. For example, those who are more predisposed to fear will be less likely to engage in risky activities. These choices around self-selection into various environments and networks can affect outcomes of interest as well.

That does not mean that it is not worth trying to investigate the human brain. Some aspects of brain morphology can provide a window into an individuals' history. Evidence from the visual cortex of rats, for example, shows that rats from more complex environments have more synapses per neuron than those from less complex environments, showing that the brain adapts to the demands, constraints, and opportunities of given environments (Sirevaag and Greenough, 1987). People seem to show similar plasticity as well. Research has shown how experience and training can change the brain, as a famous study of juggling shows (Dragansku et al., 2004). In other words, brains change as a result of the environments to which they are exposed.

Importantly, brains are not only shaped by environments and experiences but also other people. Blais et al. (2008) showed that culture even shapes something previously thought to be as universal as facial processing. In their study, they found that while White Caucasians showed the typical attention to eyes and mouth, east Asians paid more attention to the center of the face. Jack et al. (2009) show the complexity involved in adequately accounting for cultural divergences in facial expression and recognition. They show that people from East Asia, by relying on culturally specific decoding strategies that overly persist in paying attention to the eyes, have a hard time differentiating facial expressions of fear from disgust, calling into question the purported universality involved in the recognition of the facial expression of emotion and emotion signaling. Observers can learn about meaningful cultural differences from examining divergent patterns of brain activation and comparing groups based on ethnicity, culture, etc., to help deduce and infer certain information about which aspects of social cues and emotions have been processed by individuals looking at faces and other body parts such as hand movements (Grosbras and Paus, 2006).

Problems often arise in examining as well as explaining cultural differences, however, because large swaths of the general population think and believe that genetic effects are fixed, and so most people assume that there is no point in investigating anything because even if identified, genetic effects cannot be changed. And yet, the profound plasticity of the brain over the course of development and across experiences betrays the deep naïveté in such a view.

Part of the way to overcome such incorrect perceptions involves seeking to more fully educate the population about genetic variation and what it means. It is important for the public to understand that variation between continents in genetic accounts for about 9% of variation, while 91% of

variance appears within continents. Thus, there is more variation within than between populations. However, behavior, especially culturally conditioned mating norms, can and does affect genetic structure. In cultures that commonly practice cousin marriage, for example, especially first cousin marriage, children display high levels of homozygosity, leading to a much higher prevalence of disease. This can prove very expensive from a public health standpoint. Furthermore, much of variation at the level of expression does not result from genetic causes; epigenetic processes control and regulate such of this expression, especially over the course of time, suggesting a strong environmental modulation of gene expression over time (Fraga et al., 2005).

It is early days in seeking to understand these processes, but scholars need a more careful evaluation of what factors contribute to such variation in expression. Epigenetics studies offer very few cases of transgenerational phenomenon. So how can scholars begin to determine the modes of transmission for complex cultural phenomena that do not appear to have a genetic basis, such as religion? When the majority of the genome does not code for structure, and the majority of genes under positive natural selection regulate the operation of other genes, scholars need to figure out how genetic transmission affect the rules by which epigenetic processes operate.

With regard to the positive effects of natural selection, there is a difference between knowing that some feature or factor affects fitness and knowing how it works. Where does it originate? What are the circumstances in which it was originally adaptive? How does it translate across generations or ecologies? Epigenetics could be important in connecting maternal effects across generations, but how would might epigenetics affect time scale across generations? Such factors would have to depend, at least in part, on the stability and regularity of environments, and the consistency with which environmental cues and triggers signaled particular challenges, contingencies, incentives, and outcomes. Culture becomes important because it helps program us about what to do in particular environments. However, if people rely on such environmental stability to make choices, and those circumstances shift, then the foundational mechanism for making decisions will atrophy over time.

When scholars typically examine a locus of selection to investigate mechanisms of genetic transmission, the focus is on DNA and its relationship to some outcome, disease, or behavior. In this sense, genetic analysis is traditionally applied to a contiguous stretch of DNA, and functionally focused on a locus of selection. But precisely because of the vast degree of neural complexity and plasticity involved in gene–environment interaction, we need to broaden the public understanding of what a gene is. Genetic inheritance is complex, and the mechanisms that allow genes to be expressed, including the vast array of epigenetic mechanisms, not just the identification of base pair sequences, need to be incorporated into our explanations. And from this perspective, culture becomes a form of epigenetic sequence. Cognition extends to the environment, and functionality of behaviors within a given cultural context can prove very important for survival.

In examining the effect of culture on genetic transmission, and exploring the interaction between genes and environment, one of the key questions revolves around exactly how plastic is the human genome? Does culture affect its plasticity? Cultural influences do not require gene plasticity, but self-selection of individuals into particular environments or social networks as a result, in part, of genetic dispositions can influence the ways that various culture forms redound within any given individual's biology.

Some complications can arise as a result of these influences, however. It is possible, for example, to have the same environment in which two different populations exist and thus end up with different responses. Lactose intolerance provides but one example of this phenomenon demonstrating that coevolution can happen without necessarily inviting determinism; lactose tolerance was not preserved in Mongolia despite dairy in the form of yogurt and cheese remaining important dietary staples. The same genotype can produce different phenotype selections within a population, just as different adaptations can sometimes result in the same effect.

In short, while structural DNA may code for amino acids that make exons that make protein, and may be the most difficult to change, other regulatory factors such as epigenetic processes are where most of the action is precisely because it is these mechanisms that help determine what aspects of the genetic code are expressed or not in any given context. Note that the same genes that help explain current variation in some outcome of interest need not be the same ones that caused the historical variation in those outcomes. In this way, proper characterization of descriptive expression alone, while important, cannot provide the foundational basis for the development of accurate causal models.

CULTURAL PRACTICES AND LONG-TERM EFFECTS ON GENE EXPRESSION AND EPIGENETIC PROCESSES

We can learn a great deal about gene–environment interplay in the context of developing humans from examining their development in nonhuman primates. In this area, Steve Suomi and colleagues have conducted some truly remarkable and enlightening work to examine the effect of parenting behavior on social adjustment in monkeys

(Harlow and Suomi, 1971, 1974; Mineka and Suomi, 1978; Newman et al., 2005; Suomi and Harlow, 1972; Suomi, 1991, 2006; Suomi et al., 1970, 1975, 1976).

In naturalistic settings, individual differences in temperament, genes, and environment interact to shape individual developmental trajectory in monkeys, just as in humans. In some illuminating work, some infant rearing practices were manipulated. When this happened, 20% of the monkeys demonstrated fear in the face of novel stimuli, and they showed elevated levels of cortisol as measured in their hair. Such responses had a highly heritable component, and uptight monkeys were at risk for depression and anxiety disorders. In addition, 5% showed impulsivity and would do stupid things socially, which would elicit aggression, showing inappropriate aggression as well. Elevated aggression showed biological characteristics as well, including deficits in serotonin metabolism.

These monkeys live in large social groups called troops that exhibit the same basic social structures. Several have matrilineal family groups where the males leave at puberty, and all males then work their way into other troops. In rhesus monkeys, multiple dominance hierarchies exist in each troop, and within each family by age. Hierarchy in males within a troop is based on seniority, but it really revolves around alliances, with high-ranking females being the ones who carry real clout within group. Therefore, hierarchy among infants roughly reflects the position of their mother. Therefore, these monkeys need to keep the recent social history of their troop straight to keep track of their own social hierarchy. Monkeys who are good at doing this, do well in the group; otherwise, they do not survive. For the first month after birth, monkeys remain in constant contact with their mother and form an attachment bond, which they then use to explore from this secure base. About 20% remain with their mother at 6 months. During this period, the presence of the mother is very important to the monkey, and the infant becomes quite upset if the mother is gone; the child will not explore or begin interaction with peers. This time is critical for the infant to learn to polish their behavioral skills. They develop problems with reproduction and problems with aggression if they are denied access to play during this period. Because monkeys copulate year round, most infants have many peers available.

In these experiments, some monkeys were taken from their mothers and reared in a nursery with other monkeys like themselves until they reached about 6–7 months old, when they were then put back in with mother-reared kids. Monkeys raised in peer environments developed hyperattachments to each other and displayed other dysfunctions; they showed less exploration than mother-reared monkeys, and their play repertoires were never as intense or complex as mother-reared infants. Moreover, peer-raised infants proved more fearful, and they displayed elevated cortisol under conditions of challenge; they were more impulsive and aggressive, and they showed deficits in serotonin, with less serotonin binding, and more alcohol consumption. In short, such monkeys appear to provide an animal model for the development of anxiety, depression, substance abuse, and attachment disorders in humans. Further, they showed structural and functional differences in their brains in areas affecting behavioral and emotional regulation. Upon genome-wide association tests, these monkeys displayed many genes that were differentially less methylated than genetically identical mother-reared monkeys. Overall, peer-raised monkeys showed a difference in 4400 genes in their chromosomes, representing one-fifth of their entire genome. Most of these differences appeared in serotonin, hypothalamic-pituitary-adrenal (HPA) axis, and vasopressin levels but not in T cells in the immune system. In short, early rearing affected everything in gene expression. In addition, there were some notable sex differences in behavioral output, with females more anxious after puberty, but not before, and males more aggressive overall than mother-raised infants.

So, if early environments are really important in determining overall main effects on a wide variety of behavioral and emotion regulation outcomes, even affecting differential methylation, what is going on in good mothering? In short, good mothering involves intense face-to-face gazing and interaction and lip-smacking with infants. These behaviors begin to drop out around 3 weeks of age when the infant begins to explore social world. In short, good mothering provides buffering, while bad mothering (ie, those mothers who did not engage in such interactive behaviors) produced children who appeared indistinguishable from peer-raised monkeys. Interestingly, some monkeys appear to be able to overcome bad parenting if they are put in a stable supportive environment, especially during puberty.

Culture and Gene Regulation in Humans

Why can you run an experiment with monkeys and see huge effect and, by contrast, in free-range human beings get few effects? Where is the heritability? The major reason for this variability lies in the fact that experiments can be very powerful in stabilizing experience. But experience is often highly regulated, and humans are great at being masters of our own species. Humans optimize phenotypes. We often use the same phenotypes to reshape our environments, and our capacity to do so often depends on the ability of the environment to change our biology in response to local ecological constraints and opportunities. In addition, we can use our internal individual changes to self-select into different environments. These choices will not necessarily reverse our evolutionary heritage, but this ability to overcome our own evolutionary history does mean humans can

play with, and like, instrument differently than one other, and still end up with same song even though each person produces their own song in it different way with different tones and pitches.

One of the amazing ways in which we achieve a sense of consistency with ourselves over time is that we often experience ourselves, on a day-to-day basis, barring injury or illness, as being the same person living in the same body, on average. In fact, there is a rather huge discontinuity between how we experience our bodies as stable biological worlds, in the world but separate from it, and the reality that in fact our bodies are fluid and permeable. The basis for such fluidity lies in the fact that the typical half-life of protein is about 80 days, which means that for every day of life, we each have to replace 1% of ourselves. We are not the constant physical being we often experience ourselves to be; rather, we are continually in the process of regenerating ourselves. How does this happen? It happens through the regulated expression of genes, but that process is highly contingent. Just because you have genes does not mean each one is actively at work every instant. Stretches of DNA get transcribed to become RNA, which then builds proteins that influence behavior. And indeed, fluidity comes from that experience, although most genes are silent, and while we most often experience the self as stable and independent, the molecular self is fluid and permeable. But this fluidity and constant regeneration allows the capacity for various aspects of the environment to get into and change the body. And the social environment can also serve to regulate gene expression. Not all genes are on most of the time; indeed, most genes are off most of time, and they need to be turned on by some environmental exigency, internal or external, to operate. While there is some logic to the notion that genes make up the self, some of these genes are necessarily responsive to the environment, and the social environment in particular changes the expression of genes.

In other words, social interaction helps shape body, and social isolation causes many difficulties in basic biological processes as a result. Indeed, subjective social isolation has an effect on gene expression in the immune system (Cole et al., 2007). This process of social isolation works in profound and pervasive ways to inform individuals about their environment through the body. In this way, social indicators and processes provide a signal transduction pathway by which an individual comes to recognize whether they face an environment of threat or safety, abundance or deprivation, support or abuse. This information travels down through the central nervous system; indeed, this is precisely the kind of information regarding threat and safety that brains were made to understand and interpret. Brains were built precisely so that human biology could respond to threats defensively. But as George Kelley and Harry Stack Sullivan noted long ago, subjective construal is key to everything, because it is only through such subjective construal, mediated by culture, that the nature of threat or safety can be properly assessed within a given social environment and specific ecological setting.

This is the reason why we often do not find relationships between observed behavioral differences and reported (or, more likely, self-reported) factors. What is perceived is more critical to biological signaling than what appears objective. In addition, there is also often a bias in self-report. Therefore, much of what exists in people's heads does not appear in observable behaviors. Indeed, that is often why we use fMRI to help us assess what is going on in people's heads when they make decisions. They need not be lying to be incapable of accessing all the many processes that occur between perception and response. Social roles regulate the genome in incredible, complex ways: receptors talk to transcription factors; many talk to more than one; there is a high degree of network complexity that gets delivered back to the genome. This means if you can remodel a stream of information at time 1 and change its characteristics, the events at time 1 can literally restructure who you are. Those proteins hang around for 80 days, leaving you a slightly different person, exhibiting a slightly different response to the world. This means that your reaction to a different environmental stimulus at time 2 is different than it would be had you encountered it before time 1, or had someone else with a different life history encountered it at time 2 (Cole, 2009). Thus, personal history becomes a self-generating process at both a biological and molecular level, constituting a recursive developmental model. Just as evolution represents a history of the species, personal gene expression embodies the evolution of DNA gene expression profiles and offers an adaptive history of the personal environmental flux we are confronting.

In this way, social experience can remodel experience through a process of recursive regeneration. For example, Miller et al. (2009) show that children who grow up in lower socioeconomic circumstances show increase risk of many forms of chronic illness in their 50s and 60s as a result of basic biological defenses than children who grow up in richer environments. What proves adaptive in one situation might not work in another. For example, children who are more sensitive to angry faces might benefit in violent neighborhoods, while such tendencies might predispose those same individuals for greater risk of depression and anxiety later in life. Sloan et al. (2007) demonstrate how social stress provides a plausible mechanism by which environmental inputs modulate the functioning of the immune system in response to pathogen threat. Weaver et al. (2006) show that, as with Steve Suomi's monkeys, maternal care provides another environmental input that can affect mood in adulthood. They find that social factors can remodel gene expression that leaves fingerprints on the biology of organisms in the future. This process is

surprisingly enduring and happens surprisingly fast. Therefore, lifestyle looms large in the kinetic response to stress.

On the other hand, such effects can exert remarkable persistence. As Miller et al. (2009) and others demonstrate, the effects of past socioeconomic status can dominate current SES, and the residual fingerprints of past social assault can leave enduring effects.

In effect, within this model, culture expresses itself as a central nervous system–mediated interpretation of environment. Culture provides context for the psychological mediators such as threat, uncertainty or social isolation which culture can regulate through its effect on neural responses to environmental stimuli. With disadvantageous upbringing and developmental imprinting that portends a dangerous, deprived, or lonely world, self-perpetuating recursions can keep individuals in a defensive psychological state with enormously detrimental physical and mental consequences in an otherwise objectively benign world. Culture transforms social phenomena like emotion and motivation into signals that follow transduction pathways across the neuroendocrine system to mediate these effects. Important avenues for future research involve further examination of which genes are most sensitive to cultural effects, as well as investigation of which features of culture are more influential on genetic structures. For example, some genetic polymorphisms might render some individuals more sensitive or more resistant to cultural influences on gene expression (Cole et al., 2010).

Just like monkeys, humans are collective social animals. We need other people, and culture provides some of the rules and norms that guide social interaction within a collective context. If culture breaks up social integration, then humans end up fighting against the basic wiring diagram we are all born with. To the extent humans are at odds with their culture, costs to mental health can accrue, even producing illness or contributing to early morbidity or mortality.

Adaptation, Embodiment, and Ecology

Humans have killed off all competitors; we are the only survivor of the genus *Homo*. As a result, we have wiped out a lot of diversity, so we need to pay attention to adaptation. We are designed to live and be in culture. Humans cannot make it alone, without culture; if an individual cannot live in culture, he peripheralizes himself, and in so doing essentially commits suicide. Humans need to make it socially to survive physically. As a result, we keep a keen eye on local ecology, assessing definable features that can be quantified.

But what is this meaning-making machine we call culture? How do we operationalize it in practice, not as scholars, but as individuals seeing to negotiate the social world? The key aspect of adaptation to local environments is the recognition that human bodies come prepared to interact with the environment. In short, to maximize prospects for survival, the individuals are born environmentally expectant; physically and genetically, the body knows that the environment is always going to have information critical for survival. As a result, we have evolved and embody a huge number of mechanisms designed to capture and utilize that information, and a series of quite sophisticated strategies designed to map information from the environment to decide what is relevant for the body's needs. Some information we do not pay attention to at all, some we use parts of, and some captivates all our attention. And various pathways exist by which each organism decides what is important and how to respond. These kind of filtering and strategizing mechanisms are critical to prioritize the stimuli that is most relevant for survival and fitness. This is because the amount of information in the world is unlimited, time is short, and resources are limited. The mind may not be able to understand and process it all, but the body has been designed and honed over evolutionary time to be able to tell us what we need to know; the body tells us all we need to know about what we have endured in life and what we need to maximize our chances for survival.

Why have bodies been designed to take on this task? What is the organism trying to do? Every person is mortal, but genes are potentially immortal, and so bodies are designed to orient adaptive expectations to maximize prospects for reproductive fitness and success. Vigilance along multiple dimensions is energetically expensive and demanding, so systems that can monitor and filter fitness-related inputs in an automatic, unconscious, privileged, and effective manner will outperform alternative designs. These goals can also overlap with conscious desires in ways that appear normal to help individuals find their place in the world and properly calibrate their added value. A panoply of diversity exists in the human species, and there are many combinatorial possibilities in which people can engage to successfully inhabit a variety of environments. And the trade-offs that individuals chose in deciding what is important to focus on in the present, as opposed to which goals to pursue in the future, become very important determinants of reproductive success.

And, indeed, there are alternative life history strategies by which different people can try to accomplish the similar goal of reproductive success. Some people are not afforded the same social skills and resources that others possess, and when individuals are not able to develop these skills, it can become a larger issue for the collective. These outcomes often follow a fetal origins process that can include the intergenerational transmission of increased risk. For example, low birth weight girls are at increased risk of depression after puberty (Worthman and Kuzara, 2005; Costello et al., 2007). This pattern is similar to that seen in

developmental risk factors for other chronic illnesses such as cardiovascular disease and diabetes. In these cases, low birth weight becomes a proxy measure for suboptimal intrauterine conditions. Adjustments that fetuses make to survive gestation may present delayed risk of later illness and depression when the person encounters stress for which they are poorly prepared to adapt because of earlier compensations made to ensure survival. In this way, low birth weight provides one measure of an individual's increased risk of environmental sensitivity. Worthman and Kuzara posit that the HPA axis operates not only to mediate immediate sources of stress, but it also works to allocate resources across the life span involving gestational, postnatal, and adult outcomes and pressures. Indeed, drawing on earlier foundational work by Whiting (1977), Worthman (2010) demonstrated how the recognition of the power of early developmental environments can be usefully integrated with knowledge of local ecological environments to help illuminate our understanding of variations both within and between populations.

These local cultural variants can have powerful and profound influences on health outcomes, for example. Drawing on earlier work examining cultural consensus by Romney et al. (1987), Dressler and Bindon (2000) examined the relationship between blood pressure and culture in African Americans in the American South. They found a strong alignment between cultural consonance social support and blood pressure. To the extent that individuals buy into their culture but do not, in turn, live up to it, depression and cardiovascular risk result. Similarly, in examining maternal risk from postpartum hemorrhage in Bangladesh, Hruschka et al. (2008) found that culture presents a menu of options for treatment whereby not one size fits all. In this way, it becomes possible to see the strong and diverse demands placed on culture itself, which has to take a wide range of individuals and allow as many as possible to grow up and make meaning for decades within society. This represents a gigantic exercise, requiring both tremendous complexity and flexibility in the functioning of culture and how alternatives are accommodated within those constraints. All cultures have to tell you how to make a life, how to meet basic daily needs, find social support, and stay on track.

Cultures are less good at providing guidance when things do not go as planned and individuals are thrown off track by their heritage, development, or experience, as could happen, for example, in the case of children forced into child soldiering. And in fact, no one has looked at the influence of historical trauma on gene expression, although interesting work has shown the risk for diabetes and other chronic illnesses among mothers who gave birth during the famine in Belgium in 1943–45; those effects have been shown to last at least across two generations (Roseboom et al., 2001). Brown et al. (2006, 2009) and Ryan et al. (2009) have developed a useful and robust scale to assess how the life history trajectory of youth including structural conditions and social processes affects important outcomes such as risk for mental illness.

Of course, individuals are not merely passive recipients of culture, so it is equally important to examine how we shape experience of our own culture actively. For example, one factor that repeatedly emerges as important for resilience is the involvement of a singular caring adult; an individual's ability to locate and make full and proper use of such a resource can prove critical to development.

Of course, individuals as well as the community of cells within any given individual face constant resource allocation challenges. At the cellular level, local circuits can be devoted to a particular task, or broader networks can be organized into different patterns to achieve different results. In this way, neural organization and adaptation can be examined in the context of such organization and the web of dependencies that constitute them. Mapping some behaviors to circuits may help uncover those that might be easier or harder to change, or where change might be more destabilizing for the whole organism depending on how neural structures work together, or shifts that may occur in the face of increased or decreased environmental resources. Moreover, different behaviors become more salient and critical at different ages, for example during puberty or childbirth. It is very important to trace the effects of such critical periods on the way in which changes to resources may prove more or less disruptive to the overall organism.

Of course, none of this is to say that the genes themselves are irrelevant. Indeed, founder effects are important, as is genetic drift, in explaining genetic differences in populations. But cultural adaptation to such differences also exerts a critical force. In this way, populations get stuck with a set of gene frequencies and then they have to adapt to those changes in ways that are not selective. Cultural responses can help develop better adaptations to facilitate effective intersocial interaction with regard to some particular predispositions as opposed to others. In other words, culture can modify the effect of genes. Genes may represent the cards we are dealt, but culture provides the games you play with those cards. And if you miss your allocation of cards from the start, either as a result of biology or environment, you may not be able to find or buy others later on, and thus may be left out of the important reproductive game altogether.

In sum, cultural and developmental context and gene expression represent important and complex processes. And developmental time frames can prove especially critical. In a complex world, everything is always changing, and our response to those changes also depends on genetic expression. Thus, we need to seek to better understand the specific nature of genetic expression within

particular cultural contexts because culture can increase or decrease genetic sensitivity to a wide variety of environmental factors. Humans need to remain flexible and able to change over the course of development, while the timing and impact of genetic changes from macro to micro take place simultaneously and internally. As a result, all humans experience multiple levels of challenge in striving to increase their capacity through the various stages of development. For each individual, the goal is not identical or static. Rather, the ideal outcome takes place within a particular and specific cultural context. Huge cultural variations are not connected to genetic ones, and this means that culturally appropriate ways to respond to, and interpret, biological exigencies will differ and must be properly integrated into the particular meaning system for each culture to maximize health and reproductive success. Each individual has to decide what behavior they need to undertake, and understand what that behavior means given their preferred outcome. That is the essence of adaptation within the context of culture−gene coevolution.

INTERACTION OF CULTURE AND DEVELOPMENT

Human behavior takes place across multiple levels of analysis that need to be integrated to provide a more comprehensive understanding of development across the life span. As noted earlier, multiple levels of organization can produce parallel convergence. And emergent organization can result from the reciprocal determinism that engages both biology and culture.

Genes are selected by environments, even across the course of a single lifetime. For example, testosterone level predicts sexual advances in nonhuman primates, just as the number of available women predicts the level of testosterone in nearby males. This simple illustration shows the principle of reciprocal determinism in action by demonstrating how bottom-up and top-down influences can operate simultaneously, and by showing how environmental forces affect brain function and physiology.

However, this notion of multiple determinism can prove critically difficult and problematic in undertaking the practical aspects of multilevel analysis. If, for example, multiple phenotypes combine to determine the interaction of genes, environment, and epigenetic influences in wild, the very large samples may be needed to identity small but replicable effects across a population. The risk then lies in the overgeneralization of the putative importance of a particular genetic or neural variable contributing to how things work. And a partial sample may not necessarily be representative of the large population or culture. Achieving precision in this process can take a lot of time to narrow the mapping of patterns of circuits and configurations to behavioral outcomes of interests, especially because genes, much like chemistry, can operate differently computationally when combined with others genes whose function and purpose we may not fully understand yet.

So how do social and environmental exposures get under our skin to affect our risk for illness or other outcomes? And how might culture mediate and influence that process? Culture on the ground is a very real process. Its structure affects how people respond to various constraints, incentives, opportunities, and challenges. We can change culture by changing people within culture, although that certainly may prove extremely difficult and would entail thorny political questions about who decides what to change and why. Yet culture changes itself constantly. It is continually produced and reproduced by its practitioners through many recursive processes, practices, and behavioral cascades. Many of these reproductions center around power dynamics, and they identity politics that are largely context based. Intervention designed to help children adapt more successfully might strive to take advantage of the very recursive nature of culture. Culture requires a deeper understanding of the exquisitely social manifestation of behavioral cascades. After all, culture represents a shared manifestation of representations that are embedded in deep context-specific meaning. It thereby becomes the process by which individuals engage their brain, which produces and reproduces both biological and cultural changes in tandem, and in reaction. This is the very reason why cultures in many forms can perpetuate across time and shape, manifesting both flexibility and endurance.

Examining the interaction between biology, culture, and development allows us to question what otherwise might appear the most natural to us. Yet various cultures present multiple competing messages about how to be a person. And small interventions can refocus attention through these deeply recursive processes of change. Micro-environment changes accrue benefits from the specific context in which they draw meaning; the fact that culture is deep and recursive does not mean that small interventions cannot work to improve health outcomes across generations, particularly if they are generated within and perpetuated by these deeply recursive cultural processes that produce and shift meaning across generations.

Just as the vast majority of genetic variance occurs within and not between populations, the same occurs in cultural contexts such as neighborhood research. So then the question becomes what can you do to examine the sources within culture variation and how best to explore disparities and variation within the group. What dimensions of variation should be investigated? After all, environmental events have many dimensions. How do these fit within the context of a given conceptual frame? Can scholars traction the instability of a given environment to help sort people by how genotype influences them and offer

purchase on potentially buffering aspects of psychosocial development? Additional challenges occur because outcomes associated with risk and resilience vary with timing and environment; being poor when an individual is young appears to matter more for important outcomes such as educational achievement. Early poverty can impose weight for life.

Similarly, events that occur later in life can also affect meaningful biological outcomes as well. For example, status matters in achieving health. In the famous Marmot et al. (1991) Whitehall study of civil servants in England involving the exact same good health care system, all cause morbidity and mortality outcomes varied as a function of status. Furthermore, such differences later in life could be accounted for by the social class of the individual at age 5.

From a research perspective, the question then becomes how to tie the brain, culture, and behavior together to explain larger cultural variations within groups rather than simply between groups. Many cultural changes are exogenously imposed, and it might be possible to take advantage of exogenous changes to look at the interaction between brains and environment. Obviously, culture must have genetic basis, but genes function in such a way that they interact with culture. And, as noted before, specific types of genes have founder effects that produce path dependency cascades within certain individuals and contexts and provide background for certain cultures to sustain themselves across time and space. Coevolution between genes and culture happens precisely because of this deep and mutually recursive interaction of genes and environments. In this way, different evolutionary contexts and ecologies make it possible to create different cultures that develop in certain times and places as guided by specific ecological and environmental pressure.

However, once instantiated, these cultures can take on a life of their own and replicate independent of the original forces that may have help co-create them. Many cultural evolution processes are driven by variation. Over time, culture gets naturalized and becomes as unconscious as many biological processes such as breathing, although similar conscious attention may be able to control elements of both. However, moral investment often comes with the naturalization and institutionalization of cultural codes, and these can take on not only religious and political overtones, but they also become shaped by power dynamics and preferences among those with resources and status within societies. Hierarchies can then operate to sustain dynamic processes that serve to benefit those in positions of power, or those who hold sway over the coercive instruments of power, within necessarily redounding to others within a society. While the risk of overthrow can emerge when egalitarian norms are not enforced (Boehm and Boehm, 2009), large cultural biases such as the sexual subjugation of women can perpetuate when large numbers benefit reproductively by their maintenance.

And, indeed, lots of cultural traits become institutionalized, and certain deviations within them are sanctioned; however, the same process does not happen with genes. Humans cannot choose their parents, and early effects can have enormous and enduring impact; however, we do get to choose at least some of our social network, and even when you cannot change gene expression and methylation, some work suggests that finding a supportive social network can help overcome early deficits. However, if individuals return to bad environments, risks may return, and even healthy genetic structures may not be able to overcome these detriments.

CONCLUSION

New tools designed to investigate the functioning of the brain, such as functional MRI, offer potentially powerful avenues by which to explore various mental processes as they interact with environmental input. However, observers also need to remain aware of the possibility that witnessed activations are epiphenomenal, and multiple techniques need to be employed to see what is real and what is not. To inject causality to determine the unique contribution of a given region, it is important to understand the limitation of various methodologies. Otherwise, findings may just contribute to the noise. To begin to understand the complex interplay of brains, culture, and behavior, it is important to understand what is happening physiologically. What does any given signal mean? However, it also important to keep the large view in mind, and to strive to map psychophysiology and behavior to larger cultural process to begin to understand how genes map into and onto larger cultural processes.

In this way, it becomes important to map out systems. Rational models of human behavior and those driven by subconscious goals designed to maximize prospects for reproductive success are not analogous. Yet, the latter models are where the action lies. And in this regard, animal models can be useful, but it is also important to recognize the ways in which humans are distinct as well as similar to animals. Humans, for example, appear to be the only animals who are really good at imitation. Nonetheless, we can use animal modes to get at basic processes and principles that we can then test in humans for concordances and discrepancies.

In the larger exploration of the interaction between biology, genes, culture, brain, and behavior, a few recurring themes emerge across a variety of relevant species using a diverse array of methods. Child-rearing practices matter and can be used, in part, to help characterize various cultures and to make inferences about their preferred forms of social organization. If parents or children suffer from early disadvantages or detriments, those effects can last a long time, and they can be very difficult to overcome. Such individuals, in short, can have a bad time in life.

Experiencing multiple or severe traumatic early life events can produce horrible effects depending on an individual's particular genetic predisposition in interaction with the environmental circumstances they encounter. Some genetic polymorphisms serve important roles in forging culture, and many cultural practices need to be selected from a repertoire of options. Therefore, a feedback loop exists between biology and culture that can extend across a range of generations. And the evidence appears overwhelming that these processes interact in significant and decisive ways with particular parenting practices to either support or harm children within given cultural contexts.

As discussed earlier, genes are not fixed, but rather their expression remains plastic depending on various aspects of early development and cultural context. Gene by environment models to explain all kinds of behaviors and outcomes are now ubiquitous, but real biological processes can be traced back to the very molecular development of the gene and how its architecture changes in response to stimuli. Such architectural change, especially early in life, leads to changes in the gene that result from outside forces and stimuli; these effects derive in large part from culture. These effects represent environmental effects on gene expression and myelination. And these effects can be lifelong and involve the intergenerational transmission of experientially derived information. As with the Dutch mothers who gave birth during tremendous famine, and whose children and grandchildren experienced increased risk of diabetes as a result, this genetic transformation can occur in absence of the environmental input that spawned it.

Like weather, each human represents a large dynamic system that can change on a dime. There will always be a great deal of missing data as we seek to uncover and understand the complex and interactive ways in which genes, brain, behavior, and culture evolve and manifest. But, in the end, the reality is that we each exert way more control over our own biology than does our DNA. We have the ability to change the architecture of life, and personal will and character can win out over the destructive influence of negative life events every time. Culture provides each of us with a menu of options from which we can choose our behavior, and culture can shape and change our reactions to the dishes we order. But ultimately, we each have the ability and personal freedom to find our own ingredients in the form of resources and social networks that provide support and devise a recipe appropriate for the making of our own life within our own rich and unique context.

REFERENCES

Anderson, M.L., 2010. Neural reuse: a fundamental organizational principle of the brain. Behavioral and Brain Sciences 33 (04), 245–266.

Blais, C., Jack, R.E., Scheepers, C., Fiset, D., Caldara, R., 2008. Culture shapes how we look at faces. PLoS One 3 (8), e3022.

Bloom, P., 2002. Mindreading, communication and the learning of names for things. Mind & Language 17 (1–2), 37–54.

Boehm, C., Boehm, C., 2009. Hierarchy in the Forest: The Evolution of Egalitarian Behavior. Harvard University Press.

Brown, R.A., Worthman, C.M., Costello, E.J., Erkanli, A., 2006. The Life Trajectory Interview for Youth (LTI-Y): method development and psychometric properties of an instrument to assess life-course models and achievement. International Journal of Methods in Psychiatric Research 15 (4), 206–215.

Brown, R.A., Kuzara, J., Copeland, W.E., Costello, E.J., Angold, A., Worthman, C.M., 2009. Moving from ethnography to epidemiology: lessons learned in Appalachia. Annals of Human Biology 36 (3), 248–260.

Canli, T., Lesch, K.P., 2007. Long story short: the serotonin transporter in emotion regulation and social cognition. Nature Neuroscience 10 (9), 1103–1109.

Carpenter, M., Tomasello, M., 1995. Joint attention and imitative learning in children, chimpanzees, and enculturated chimpanzees. Social Development 4 (3), 217–237.

Chen, C., Burton, M., Greenberger, E., Dmitrieva, J., 1999. Population migration and the variation of dopamine D4 receptor (DRD4) allele frequencies around the globe. Evolution and Human Behavior 20 (5), 309–324.

Chiao, J.Y., Ambady, N., 2007. Cultural neuroscience: parsing universality and diversity across levels of analysis. In: Kitayama, S., Cohen, D. (Eds.), Handbook of Cultural Psychology, pp. 237–254. New York.

Chiao, J.Y., Blizinsky, K.D., 2009. Culture–gene coevolution of individualism–collectivism and the serotonin transporter gene. Proceedings of the Royal Society B: Biological Sciences. http://dx.doi.org/10.1098/rspb.2009.1650.

Chiao, J.Y. (Ed.), 2009. Cultural Neuroscience: Cultural Influences on Brain Function: Cultural Influences on Brain Function, vol. 178. Elsevier.

Chiao, J.Y., 2010. At the frontier of cultural neuroscience: introduction to the special issue. Social, Cognition and Affective Neuroscience 5, 109–110.

Cochran, G., Harpending, H., 2009. The 10,000 Year Explosion: How Civilization Accelerated Human Evolution. Basic Books.

Cole, S.W., Hawkley, L.C., Arevalo, J.M., Sung, C.Y., Rose, R.M., Cacioppo, J.T., 2007. Social regulation of gene expression in human leukocytes. Genome Biol 8 (9), R189.

Cole, S.W., Arevalo, J.M., Takahashi, R., Sloan, E.K., Lutgendorf, S.K., Sood, A.K., Sheridan, J.F., Seeman, T.E., 2010. Computational identification of gene–social environment interaction at the human IL6 locus. Proceedings of the National Academy of Sciences 107 (12), 5681–5686.

Cole, S.W., 2009. Social regulation of human gene expression. Current Directions in Psychological Science 18 (3), 132–137.

Costello, E.J., Worthman, C., Erkanli, A., Angold, A., 2007. Prediction from low birth weight to female adolescent depression: a test of competing hypotheses. Archives of General Psychiatry 64 (3), 338–344.

Dehaene, S., Pegado, F., Braga, L.W., Ventura, P., Nunes Filho, G., Jobert, A., Dehaene-Lambertz, G., Kolinsky, R., Morais, J., Cohen, L., 2010. How learning to read changes the cortical networks for vision and language. Science 330 (6009), 1359–1364.

Descartes, R., 2006. Discourse on method (1637). The Philosophical Works of Descartes 1, 92.

Draganski, B., Gaser, C., Busch, V., Schuierer, G., Bogdahn, U., May, A., 2004. Neuroplasticity: changes in grey matter induced by training. Nature 427 (6972), 311–312.

Drayton, L., Santos, L.R., 2014. Understanding interspecies variation in primate prosocial behavior: insights from capuchin monkeys (*Cebus apella*). Behavioral Sciences 4, 87–101.

Dressler, W.W., Bindon, J.R., 2000. The health consequences of cultural consonance: cultural dimensions of lifestyle, social support, and arterial blood pressure in an African American community. American Anthropologist 102 (2), 244–260.

Eisenberg, D.T., Campbell, B., Gray, P.B., Sorenson, M.D., 2008. Dopamine receptor genetic polymorphisms and body composition in undernourished pastoralists: an exploration of nutrition indices among nomadic and recently settled Ariaal men of northern Kenya. BMC Evolutionary Biology 8 (1), 173.

Fincher, C.L., Thornhill, R., 2008. Assortative sociality, limited dispersal, infectious disease and the genesis of the global pattern of religion diversity. Proceedings of the Royal Society B: Biological Sciences 275 (1651), 2587–2594.

Fincher, C.L., Thornhill, R., Murray, D.R., Schaller, M., 2008. Pathogen prevalence predicts human cross-cultural variability in individualism/collectivism. Proceedings of the Royal Society B: Biological Sciences 275 (1640), 1279–1285.

Fraga, M.F., Ballestar, E., Paz, M.F., Ropero, S., Setien, F., Ballestar, M.L., Heine-Suñer, D., Cigudosa, J.C., Urioste, M., Benitez, J., Boix-Chornet, M., Sanchez-Aguilera, A., Ling, C., Carlsson, E., Poulsen, P., Vaag, A., Stephan, Z., Spector, T.D., Wu, Y.Z., Plass, C., Esteller, M., 2005. Epigenetic differences arise during the lifetime of monozygotic twins. Proceedings of the National Academy of Sciences of the United States of America 102 (30), 10604–10609.

Green, A.E., Munafò, M.R., DeYoung, C.G., Fossella, J.A., Fan, J., Gray, J.R., 2008. Using genetic data in cognitive neuroscience: from growing pains to genuine insights. Nature Reviews Neuroscience 9 (9), 710–720.

Grosbras, M.H., Paus, T., 2006. Brain networks involved in viewing angry hands or faces. Cerebral Cortex 16 (8), 1087–1096.

Han, S., Ma, Y., 2015. A culture–behavior–brain loop model of human development. Trends in Cognitive Sciences 19 (11), 666–676.

Han, S., Northoff, G., 2008. Culture-sensitive neural substrates of human cognition: a transcultural neuroimaging approach. Nature Reviews Neuroscience 9 (8), 646–654.

Han, S., Northoff, G., Vogeley, K., Wexler, B.E., Kitayama, S., Varnum, M.E., 2013. A cultural neuroscience approach to the biosocial nature of the human brain. Annual Review of Psychology 64, 335–359.

Harlow, H.F., Suomi, S.J., 1971. Social recovery by isolation-reared monkeys. Proceedings of the National Academy of Sciences 68 (7), 1534–1538.

Harlow, H.F., Suomi, S.J., 1974. Induced depression in monkeys. Behavioral Biology 12 (3), 273–296.

Hawks, J., Wang, E.T., Cochran, G.M., Harpending, H.C., Moyzis, R.K., 2007. Recent acceleration of human adaptive evolution. Proceedings of the National Academy of Sciences 104 (52), 20753–20758.

Hein, G., Singer, T., 2008. I feel how you feel but not always: the empathic brain and its modulation. Current Opinion in Neurobiology 18 (2), 153–158.

Hirsch, H.V., Spinelli, D.N., 1970. Visual experience modifies distribution of horizontally and vertically oriented receptive fields in cats. Science 168 (3933), 869–871.

Hruschka, D.J., Sibley, L.M., Kalim, N., Edmonds, J.K., 2008. When there is more than one answer key: cultural theories of postpartum hemorrhage in Matlab, Bangladesh. Field Methods 20 (4), 315–337.

Hubel, D.H., Wiesel, T.N., 1962. Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. The Journal of Physiology 160 (1), 106–154.

Jack, R.E., Blais, C., Scheepers, C., Schyns, P.G., Caldara, R., 2009. Cultural confusions show that facial expressions are not universal. Current Biology 19 (18), 1543–1548.

Jansma, J.M., Ramsey, N.F., Van Der Wee, N.J.A., Kahn, R.S., 2004. Working memory capacity in schizophrenia: a parametric fMRI study. Schizophrenia Research 68 (2), 159–171.

Keysers, C., Gazzola, V., 2010. Social neuroscience: mirror neurons recorded in humans. Current Biology 20 (8), R353–R354.

Keysers, C., Gazzola, V., 2014. Hebbian learning and predictive mirror neurons for actions, sensations and emotions. Philosophical Transactions of the Royal Society B: Biological Sciences 369 (1644), 20130175.

Kitayama, S., Uskul, A.K., 2011. Culture, mind, and the brain: current evidence and future directions. Annual Review of Psychology 62, 419–449.

Leimgruber, K.L., Ward, A.F., Widness, J., Norton, M.I., Olson, K.R., Gray, K., Santos, L.R., 2014. Give what you get: capuchin monkeys (*Cebus apella*) and 4-year-old children pay forward positive and negative outcomes to conspecifics. PLoS One 9 (1), e87035. http://dx.doi.org/10.1371/journal.pone.0087035.

Li, S.C., 2003. Biocultural orchestration of developmental plasticity across levels: the interplay of biology and culture in shaping the mind and behavior across the life span. Psychological Bulletin 129 (2), 171.

Luo, S., Han, S., 2014. The association between an oxytocin receptor gene polymorphism and cultural orientations. Culture and Brain 2 (1), 89–107.

Luo, S., Ma, Y., Liu, Y., Li, B., Wang, C., Shi, Z., Li, X., Zhang, W., Rao, Y., Han, S., 2015. Interaction between oxytocin receptor polymorphism and interdependent culture values on human empathy. Social Cognitive and Affective Neuroscience 10 (9), 1273–1281.

Maguire, E.A., Woollett, K., Spiers, H.J., 2006. London taxi drivers and bus drivers: a structural MRI and neuropsychological analysis. Hippocampus 16 (12), 1091–1101.

Marinkovic, K., Dhond, R.P., Dale, A.M., Glessner, M., Carr, V., Halgren, E., 2003. Spatiotemporal dynamics of modality-specific and supramodal word processing. Neuron 38 (3), 487–497.

Markus, H.R., Kitayama, S., 2010. Cultures and selves A cycle of mutual constitution. Perspectives on Psychological Science 5 (4), 420–430.

Marmot, M.G., Stansfeld, S., Patel, C., North, F., Head, J., White, I., Brunner, E., Feeney, A., Smith, G.D., 1991. Health inequalities among British civil servants: the Whitehall II study. The Lancet 337 (8754), 1387–1393.

McElreath, R., Bell, A.V., Efferson, C., Lubell, M., Richerson, P.J., Waring, T., 2008. Beyond existence and aiming outside the laboratory: estimating frequency-dependent and pay-off-biased social learning strategies. Philosophical Transactions of the Royal Society B: Biological Sciences 363 (1509), 3515–3528.

Miller, G.E., Chen, E., Fok, A.K., Walker, H., Lim, A., Nicholls, E.F., Cole, S., Kobor, M.S., 2009. Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. Proceedings of the National Academy of Sciences 106 (34), 14716–14721.

Mineka, S., Suomi, S.J., 1978. Social separation in monkeys. Psychological Bulletin 85 (6), 1376.

Nagell, K., Olguin, R.S., Tomasello, M., 1993. Processes of social learning in the tool use of chimpanzees (*Pan troglodytes*) and human children (*Homo sapiens*). Journal of Comparative Psychology 107 (2), 174.

Newman, T.K., Syagailo, Y.V., Barr, C.S., Wendland, J.R., Champoux, M., Graessle, M., Suomi, S.J., Higley, J.D., Lesch, K.P., 2005. Monoamine oxidase A gene promoter variation and rearing experience influences aggressive behavior in rhesus monkeys. Biological Psychiatry 57 (2), 167–172.

Paus, T., Zijdenbos, A., Worsley, K., Collins, D.L., Blumenthal, J., Giedd, J.N., Rapoport, J.L., Evans, A.C., 1999. Structural maturation of neural pathways in children and adolescents: in vivo study. Science 283 (5409), 1908–1911.

Pinker, S., 2011. The Better Angels of Our Nature: Why Violence Has Declined, vol. 75. Viking, New York.

Richerson, P.J., Boyd, R., 2008. Not by Genes Alone: How Culture Transformed Human Evolution. University of Chicago Press.

Rogers, A.R., Harpending, H., 1992. Population growth makes waves in the distribution of pairwise genetic differences. Molecular Biology and Evolution 9 (3), 552–569.

Romney, A.K., Batchelder, W.H., Weller, S.C., 1987. Recent applications of cultural consensus theory. American Behavioral Scientist 31 (2), 163–177.

Rosati, A.G., Wobber, V., Hughes, K., Santos, L.R., 2014. Comparative developmental psychology: how is human cognitive development unique? Evolutionary Psychology 12, 448–473.

Roseboom, T.J., Van Der Meulen, J.H., Ravelli, A.C., Osmond, C., Barker, D.J., Bleker, O.P., 2001. Effects of prenatal exposure to the Dutch famine on adult disease in later life: an overview. Molecular and Cellular Endocrinology 185 (1), 93–98.

Ryan, S., Franzetta, K., Schelar, E., Manlove, J., 2009. Family structure history: links to relationship formation behaviors in young adulthood. Journal of Marriage and Family 71 (4), 935–953.

Sirevaag, A.M., Greenough, W.T., 1987. Differential rearing effects on rat visual cortex synapses.: III. Neuronal and glial nuclei, boutons, dendrites, and capillaries. Brain Research 424 (2), 320–332.

Sloan, E.K., Capitanio, J.P., Tarara, R.P., Mendoza, S.P., Mason, W.A., Cole, S.W., 2007. Social stress enhances sympathetic innervation of primate lymph nodes: mechanisms and implications for viral pathogenesis. The Journal of Neuroscience 27 (33), 8857–8865.

Suomi, S.J., Harlow, H.F., 1972. Social rehabilitation of isolate-reared monkeys. Developmental Psychology 6 (3), 487.

Suomi, S.J., Harlow, H.F., Domek, C.J., 1970. Effect of repetitive infant-infant separation of young monkeys. Journal of Abnormal Psychology 76 (2), 161.

Suomi, S.J., Eisele, C.D., Grady, S.A., Harlow, H.F., 1975. Depressive behavior in adult monkeys following separation from family environment. Journal of Abnormal Psychology 84 (5), 576.

Suomi, S.J., Collins, M.L., Harlow, H.F., Ruppenthal, G.C., 1976. Effects of maternal and peer separations on young monkeys. Journal of Child Psychology and Psychiatry 17 (2), 101–112.

Suomi, S.J., 1991. Early stress and adult emotional reactivity in rhesus monkeys. The Childhood Environment and Adult Disease 171–188.

Suomi, S.J., 2006. Risk, resilience, and gene× environment interactions in rhesus monkeys. Annals of the New York Academy of Sciences 1094 (1), 52–62.

Tomasello, M., Savage-Rumbaugh, S., Kruger, A.C., 1993. Imitative learning of actions on objects by children, chimpanzees, and enculturated chimpanzees. Child Development 64 (6), 1688–1705.

Tomasello, M., 1993. It's imitation, not mimesis. Behavioral and Brain Sciences 16 (04), 771–772.

Tomasello, M., 1999. The human adaptation for culture. Annual Review of Anthropology 509–529.

Vogt, S., Buccino, G., Wohlschläger, A.M., Canessa, N., Shah, N.J., Zilles, K., Eickhoff, S.B., Freund, H.-J., Rizzolatti, G., Fink, G.R., 2007. Prefrontal involvement in imitation learning of hand actions: effects of practice and expertise. Neuroimage 37 (4), 1371–1383.

Wang, E.T., Kodama, G., Baldi, P., Moyzis, R.K., 2006. Global landscape of recent inferred Darwinian selection for *Homo sapiens*. Proceedings of the National Academy of Sciences of the United States of America 103 (1), 135–140.

Weaver, I.C., Meaney, M.J., Szyf, M., 2006. Maternal care effects on the hippocampal transcriptome and anxiety-mediated behaviors in the offspring that are reversible in adulthood. Proceedings of the National Academy of Sciences of the United States of America 103 (9), 3480–3485.

Whiten, A., Custance, D.M., Gomez, J.C., Teixidor, P., Bard, K.A., 1996. Imitative learning of artificial fruit processing in children (*Homo sapiens*) and chimpanzees (*Pan troglodytes*). Journal of Comparative Psychology 110 (1), 3.

Whiting, J.W., 1977. A model for psychocultural research. Culture and Infancy: Variations in the Human Experience 29–48.

Worthman, C.M., Kuzara, J., 2005. Life history and the early origins of health differentials. American Journal of Human Biology 17 (1), 95–112.

Worthman, C.M., Plotsky, P.M., Schechter, D.S., Cummings, C.A. (Eds.), 2010. Formative Experiences: The Interaction of Caregiving, Culture, and Developmental Psychobiology. Cambridge University Press.

Worthman, C.M., 2010. The ecology of human development: evolving models for cultural psychology. Journal of Cross-Cultural Psychology 41 (4), 546–562.

Zhang, D., Raichle, M.E., 2010. Disease and the brain's dark energy. Nature Reviews Neurology 6 (1), 15–28.

Zhu, Y., Zhang, L., Fan, J., Han, S., 2007. Neural basis of cultural influence on self-representation. Neuroimage 34 (3), 1310–1316.

Part III

Ethics, Politics and Religious Considerations

Chapter 35

Adaptive Significance of Ethics and Aesthetics

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There is grandeur in this view of life, with its several powers, having been originally breathed into a few forms or into one; and that, whilst this planet has gone cycling on according to the fixed law of gravity, from so simple a beginning endless forms most beautiful and most wonderful have been, and are being, evolved.

Charles Darwin, *On the Origin of Species* [1859, p. 490, first ed.]

I fully subscribe to the judgment of those writers who maintain that, of all the differences between man and the lower animals, the moral sense or conscience is by far the most important.

Charles Darwin, *The Descent of Man* [1871, Chapter 3, p. 67]

INTRODUCTION

Ethics is a human universal. People have moral values: that is, they accept standards according to which their conduct is judged: either right or wrong, or good or evil. The particular norms by which moral actions are judged vary to some extent from individual to individual, and from culture to culture (although some norms, like not to kill, not to steal, and to honor one's parents, are widespread and perhaps universal), but value judgments concerning human behavior are passed in all cultures. This universality raises the questions whether the moral sense is part of human nature, one more dimension of our biological makeup; and whether ethical values may be the product of biological evolution, rather than being given by religious and cultural traditions.

I will define moral behavior for the present purposes as the actions of a person who takes into account in a sympathetic way the impact the actions have on others. A related definition is advanced by David Copp in *The Oxford Handbook of Ethical Theory* (2006, p. 4): "[W]e can take a person's moral beliefs to be the beliefs she has about how to live her life when she takes into account in a sympathetic way the impact of her life and decisions on others." Altruism may be defined in a similar way as, for example, "unselfish regard for or devotion to the welfare of others" (*Webster's New Collegiate Dictionary*, 10th ed.). Altruism, however, is usually taken to imply some cost to the altruist for the benefit of others, and this is the sense in which "altruism" will be used here. I will use the term "ethical behavior" as a synonym of "moral behavior," and "morality" and "ethics" as synonyms of each other, except when explicitly noted or contextually obvious that they are used with a somewhat different meaning. Some authors use morality or "virtue ethics" in a broader sense that would include good feelings in regard to others and that exclude inappropriate thoughts or desires, such as entertaining sexual desires for somebody else's wife or wishes that something harmful would happen to others. So long as these thoughts or desires are not transformed into actions, they will not be included in my use of morality. Actions that may be thought to be evil or sinful in some moral systems, such as masturbation, will not be included either in my use of morality, so long as the actions have no consequences for others.

There are many theories concerned with the rational grounds for morality, such as deductive theories that seek to discover the axioms or fundamental principles that determine what is morally correct on the basis of direct moral intuition; or theories, such as like logical positivism or existentialism that negate rational foundations

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00035-1

of morality, reducing moral principles to social decisions or to emotional and other irrational grounds. After the publication of Darwin's theory of evolution by natural selection, several philosophers as well as scientists attempted to find in the evolutionary process the justification for moral behavior.

Aristotle and other philosophers of classical Greece and Rome, as well as many other philosophers throughout the centuries, held that humans hold moral values by nature. A human is not only *Homo sapiens*, but also *Homo moralis*. But biological evolution brings about two important issues: timing and causation. We do not attribute ethical behavior to animals (surely, not to all animals and not to the same extent as to humans, in any case). Therefore, evolution raises distinctive questions about the origins and tenets of moral behavior. When did ethical behavior come about in human evolution? Did modern humans have an ethical sense from the beginning? Did Neandertals hold moral values? What about *Homo erectus* and *Homo habilis*? And how did the moral sense evolve? Was it directly promoted by natural selection? Or did it come about as a by-product of some other attribute (such as rationality) that was the direct target of selection? Alternatively, is the moral sense an outcome of cultural evolution rather than of biological evolution?

DARWIN AND THE MORAL SENSE

Two years after returning from his trip in the HMS *Beagle* (1826–1831), Darwin began gathering contemporaneous literature on human moral behavior, including such works as William Paley's *The Principles of Moral and Political Philosophy* (1785), which he had encountered earlier while a student at the University of Cambridge, and the multivolume *Illustrations of Political Economy* by Harriet Martineau, published in 1832–1834. These two authors, like other philosophers of the time, maintained that morality was a conventional attribute of humankind, rather than a naturally determined human attribute, using an argument often exploited in our days: the diversity of moral codes.

The proliferation of ethnographic voyages had brought to light the great variety of moral customs and rules. This is something Darwin had observed in South America among the Indian populations. But this apparent dispersion had not distracted him. He would eventually develop a more complex and subtle theory of the moral sense than those contemporaneous authors; a theory that, implicitly at least, recognized moral behavior as a biologically determined human universal but with culturally evolved differences. For Darwin the ethnographic diversity of moral customs and rules came about as an adaptive response to the environmental and historical conditions, unique in every different place, without necessarily implying that morality was an acquired rather than natural human trait.

A variable adaptive response could derive from some fundamental capacity: a common substrate unique for the whole human race but capable of becoming expressed in diverse directions. Darwin did not attribute the universality of morality to supernatural origin, but rather saw it as a product of evolution by natural selection. The presence of a universal and common foundation, endowing humans with an ethical capacity, was for Darwin compatible with different cultures manifesting different stages of moral evolution and with different sets of moral norms.

Darwin's first sustained discussion of morality is in chapter 3 of *The Descent of Man* (1871, pp. 67–102), and his two most significant points concerning the evolution of morality are stated early in the chapter: (1) that moral behavior is a necessary attribute of advanced intelligence as it occurs in humans, and thus that moral behavior is biologically determined; and (2) that the norms of morality are not biologically determined but a result of human collective experience, or human culture as we would now call it.

After the two initial paragraphs of Chapter 3, which assert that the moral sense is the most important difference "between man and the lower animals" (see quotation from earlier in this chapter), Darwin states his view that moral behavior is strictly associated with advanced intelligence: "The following proposition seems to me in a high degree probable—namely, that any animal whatever, endowed with well-marked social instincts, would inevitably acquire a moral sense or conscience, as soon as its intellectual powers had become as well developed, or nearly as well developed, as in man" (pp. 68–69). Darwin is affirming that the moral sense, or conscience, is a necessary consequence of high intellectual powers, such as exist in modern humans. Therefore, if our intelligence is an outcome of natural selection, the moral sense would be as well an outcome of natural selection. Darwin's statement further implies that the moral sense is not by itself directly promoted by natural selection but only indirectly as a necessary consequence of high intellectual powers, which are the attributes that natural selection is directly promoting.

MORAL BEHAVIOR VERSUS MORAL NORMS

Darwin also states that even if some animal could achieve a human-equivalent degree of development of its intellectual faculties, we cannot conclude that it would also acquire exactly the same moral sense as ours. "I do not wish to maintain that any strictly social animal, if its intellectual faculties were to become as active and as highly developed as in man, would acquire the same moral sense as ours…

[T]hey might have a sense of right and wrong, though led by it to follow widely different lines of conduct" (Darwin, 1871, p. 70). These statements imply that, according to Darwin, having a moral sense does not by itself determine what the moral norms would be: which sorts of actions might by sanctioned by the norms and which ones would be condemned.

This distinction is important. Indeed, it is a distinction central to the theory I will be advancing herein. Much of the historical controversy, particularly between scientists and philosophers, as to whether the moral sense is or is not biologically determined has arisen owing to a failure to make the distinction. Scientists often affirm that morality is a human biological attribute because they are thinking of the predisposition to pass moral judgment: that is, to judge some actions as good and others as evil. Some philosophers, such as William Paley and Harriet Martineau, as well as many contemporary philosophers, argue that morality is not biologically determined, but rather comes from cultural traditions or from religious beliefs, because they are thinking about moral codes, the sets of norms that determine which actions are judged to be good and which are evil. They point out that moral codes vary from culture to culture and, therefore, are not biologically predetermined.

I consider this distinction fundamental (Ayala, 1987, 2010). Thus, I'll argue that the question of whether ethical behavior is biologically determined may refer to either one of the following two issues. First, is the capacity for ethics—the proclivity to judge human actions as either right or wrong—determined by the biological nature of human beings? Second, are the systems or codes of ethical norms accepted by human beings biologically determined? A similar distinction can be made with respect to language. The question whether the capacity for symbolic creative language is determined by our biological nature is different from the question whether the particular language we speak—English, Spanish, Chinese, etc.—is biologically determined, which in the case of language obviously it is not.

The distinction between the predisposition to judge certain sorts of actions as either morally good or evil and the norms according to which we determine which actions are good and which actions are evil, has affinity with the distinction made by moral philosophers between metaethics and normative ethics. The subject of metaethics is why we ought to do what we ought to do, while normative ethics tells us what we ought to do. I will propose that the moral evaluation of actions emerges from human rationality, or, in Darwin's terms, from our highly developed intellectual powers. Our high intelligence allows us to anticipate the consequences of our actions with respect to other people and, thus, to judge them as good or evil in terms of their consequences for others. But I will propose that the norms according to which we decide which actions are good and which actions are evil are largely culturally determined, although conditioned by biological predispositions.

DARWINIAN AFTERMATH

Herbert Spencer (1820–1903) was among the first philosophers seeking to find the grounds of morality in biological evolution. In *The Principles of Ethics* (1893), Spencer seeks to discover values that have a natural foundation. Spencer argues that the theory of organic evolution implies certain ethical principles. Human conduct must be evaluated, like any biological activity whatsoever, according to whether it conforms to the life process; therefore, any acceptable moral code must be based on natural selection, the law of struggle for existence. According to Spencer, the most exalted form of conduct is that which leads to a greater duration, extension, and perfection of life; the morality of all human actions must be measured by that standard. Spencer proposes that, although exceptions exist, the general rule is that pleasure goes with that which is biologically useful, whereas pain marks what is biologically harmful. This is an outcome of natural selection; thus, while doing what brings pleasure and avoiding what is painful, organisms improve their chances for survival. With respect to human behavior, we see that we derive pleasure from virtuous behavior and pain from evil actions, associations which indicate that the morality of human actions is also founded on biological nature.

Spencer proposes as the general rule of human behavior that anyone should be free to do anything that they want, so long as it does not interfere with the similar freedom to which others are entitled. The justification of this rule is found in organic evolution: the success of an individual, plant, or animal depends on its ability to obtain that which it needs. Consequently, Spencer reduces the role of the state to protecting the collective freedom of individuals so that they can do as they please. This laissez-faire form of government may seem ruthless, because individuals would seek their own welfare without any consideration for others (except for respecting their freedom), but Spencer believes that it is consistent with traditional Christian values. It may be added that, although Spencer sets the grounds of morality on biological nature and on nothing else, he admits that certain moral norms go beyond that which is biologically determined; these are rules formulated by society and accepted by tradition.

Social Darwinism, in Spencer's version or in some variant form, was fashionable in European and American circles during the latter part of the 19th century and the early years of the 20th century, but it has few or no

distinguished intellectual followers at present. Spencer's critics include the evolutionists Julian Huxley and C.H. Waddington, who, nevertheless, maintain that organic evolution provides grounds for a rational justification of ethical codes. For Julian Huxley (1953; Huxley and Huxley, 1947), the standard of morality is the contribution that actions make to evolutionary progress, which goes from less to more advanced organisms. For Waddington (1960), the morality of actions must be evaluated by their contribution to human evolution.

Huxley and Waddington's views are based on value judgments about what is or is not progressive in evolution. But, contrary to Huxley's claim, there is nothing objective in the evolutionary process itself (ie, outside human considerations; see Ayala, 1982, 1987; and Chapter 34 in this book) that makes the success of bacteria, which have persisted as such for more than 2 billion years and which consist of a huge diversity of species and astronomic numbers of individuals, less desirable than that of the vertebrates, even though the latter are more complex. The same objection can be raised against Waddington's human evolution standard of biological progress. Are the insects, of which more than one million species exist, less desirable or less successful from a purely biological perspective than humans or any other mammal species? Waddington fails to demonstrate why the promotion of human biological evolution by itself should be the standard to measure what is morally good.

Numerous philosophers as well as scientists have sought to give accounts of moral behavior as an evolutionary outcome (eg, Ayala and Arp, 2010; Blackmore, 1999; Hauser, 2006; Maienschein and Ruse, 1999; Ruse, 1995; Sober and Wilson, 1998; Wilson, 2012). Particularly notable are the contributions of Edward O. Wilson (1975, 1978, 1998), founder of sociobiology as an independent discipline engaged in discovering the biological foundations of all social behavior. Wilson and other sociobiologists, as well as the derivative subdisciplines of evolutionary psychology (eg, Barkow et al., 1992) and memetics (Blackmore, 1999), have sought to solve the naturalistic fallacy by turning it on its head. They assert that moral behavior does not exist as something distinct from biological, or biologically determined, behavior. As Ruse and Wilson (1985) have asserted, "Ethics is an *illusion* [italics added] put in place by natural selection to make us good cooperators" (p. 50). I shall return later to these sociobiological and related proposals.

MORAL BEHAVIOR AS RATIONAL BEHAVIOR

The first proposition I will advance here, fully consistent with Darwin's ideas, is that humans, because of their high intellectual powers, are necessarily inclined to make moral judgments and to accept ethical values: that is, to evaluate certain kinds of actions as either right or wrong. The claim I make is that moral behavior is a necessary outcome of the biological makeup of humans, a product of their evolution. This view would fall within the metaethical theories known as deontological or rational. It is the exalted degree of rationality that we humans have achieved that makes us moral beings. Humans are *Homo moralis* because they are *Homo rationalis*.

This thesis does not imply that the norms of morality are also biologically determined or that they are unambiguous consequences of our rationality. Independent of whether or not humans have a biologically determined moral sense, it remains to be ascertained whether particular moral prescriptions are in fact determined by the biological nature of humans or whether they are products of cultural evolution, either chosen by society or established by religious beliefs, or even selected according to individual preferences. Even if we were to conclude that people cannot avoid having moral standards of conduct, it might be that the choice of the particular standards used for judgment would be arbitrary or a product of cultural evolution. The need for having moral values does not necessarily tell us what the moral values should be, like the capacity for language does not determine which language we shall speak.

I will first argue that humans are ethical beings by their biological nature: that humans evaluate their behavior as either right or wrong, moral or immoral, as a consequence of their eminent intellectual capacities, which include self-awareness and abstract thinking. These intellectual capacities are products of the evolutionary process, but they are distinctively human. Thus, I will assert that ethical behavior is not causally related to the social behavior of animals, including kin selection and the so-called "reciprocal altruism."

A second argument that I will put forward is that the moral norms according to which we evaluate particular actions as either morally good or morally bad (as well as the grounds that may be used to justify the moral norms) are products of cultural evolution, not of biological evolution. The norms of morality belong, in this respect, to the same category of phenomena as political and religious institutions, or the arts, sciences, and technology, as well as the particular languages we speak. The moral codes, like these other products of human culture, are often consistent with the biological predispositions of the human species. But many moral norms are formulated independently of biological necessity or predisposition, simply because they do not have necessary biological consequences. Biological welfare (survival and reproduction) is not obviously determinant of all ethical norms in any given society or culture.

Moral codes, like any other cultural system, depend on the existence of human biological nature and must be consistent with it, in the sense that they could not counteract it without promoting their own demise. Moreover, the acceptance and persistence of moral norms is facilitated whenever they are consistent with biologically conditioned human behaviors. But the moral norms are independent of such behaviors in the sense that some norms may not favor, and may hinder, the survival and reproduction of the individual and its genes, which processes are the targets of biological evolution. Discrepancies between accepted moral rules and biological survival are, however, necessarily limited in scope or would otherwise lead to the extinction of the groups accepting such discrepant rules.

CONDITIONS FOR ETHICAL BEHAVIOR

I will now refer to the *moral sense* in its strict meaning as the evaluation of some actions as virtuous, or morally good, and others as evil, or morally bad. Morality in this sense is the urge or predisposition to judge human actions as either right or wrong in terms of their consequences for other human beings. In this sense, humans are moral beings by nature because their biological constitution determines the presence in them of the three necessary conditions for ethical behavior. These conditions are (1) the ability to anticipate the consequences of one's own actions; (2) the ability to make value judgments; and (3) the ability to choose between alternative courses of action. These abilities exist as a consequence of the eminent intellectual capacity of human beings. Notice, as I will discuss further, that I am not taking the position known as utilitarianism, because I am not claiming that maximizing the benefits to others, and to as many others as possible, is the ultimate standard by which the morality of actions should be determined.

The ability to anticipate the consequences of one's own actions is the most fundamental of the three conditions required for ethical behavior. Only if I can anticipate that pulling the trigger will shoot the bullet, which in turn will strike and kill my enemy, can the action of pulling the trigger be evaluated as nefarious. Pulling a trigger is not in itself a moral action; it becomes so by virtue of its relevant consequences. My action has an ethical dimension only if I do anticipate these consequences.

The ability to anticipate the consequences of one's actions is closely related to the ability to establish the connection between means and ends: that is, of seeing a means precisely as a means, as something that serves a particular end or purpose. This ability to establish the connection between means and their ends requires the ability to anticipate the future and to form mental images of realities not present or not yet in existence.

The ability to establish the connection between means and ends happens to be the fundamental intellectual capacity that has made possible the development of human culture and technology. An evolutionary scenario, seemingly the best hypothesis available, proposes that the remote evolutionary roots of this capacity to connect means with ends may be found in the evolution of bipedalism, which transformed the anterior limbs of our ancestors from organs of locomotion into organs of manipulation. The hands thereby gradually became organs adept for the construction and handling of objects for hunting and other activities that improved survival and reproduction: that is, which increased the reproductive fitness of their carriers. Eventually, our ancestors of about 2 Ma advanced from using as tools existing objects, such as a stone or a wooden stick, to making tools themselves. The construction of tools depends not only on manual dexterity, but on perceiving them precisely as tools, as objects that help to perform certain actions—that is, as means that serve certain ends or purposes: a knife for cutting, an arrow for hunting, an animal skin for protecting the body from the cold. According to this evolutionary scenario, natural selection promoted the intellectual capacity of our bipedal ancestors because increased intelligence facilitated the perception of tools as tools, and therefore their construction and use, with the ensuing amelioration of biological survival and reproduction.

The development of the intellectual abilities of our ancestors took place over several million years, gradually increasing the ability to connect means with their ends and, hence, the possibility of making ever more complex tools serving more remote purposes. According to the theory I am proposing, the ability to anticipate the future, essential for ethical behavior, is therefore closely associated with the development of the ability to construct tools, an ability that has produced the advanced technologies of modern societies and that is largely responsible for the success of humans as a biological species.

The second condition for the existence of ethical behavior is the ability to make value judgments, to perceive certain objects or deeds as more desirable than others. Only if I can see the death of my enemy as preferable to his survival (or vice versa) can the action leading to his demise be thought of as moral. If the consequences of alternative actions are neutral with respect to value, an action cannot be characterized as ethical. Values are of many sorts: not only ethical, but also aesthetic, economic, gastronomic, political, and so on. But in all cases, the ability to make value judgments depends on the capacity for abstraction: that is, on the capacity to perceive actions or objects as members of general classes. This makes it possible to compare objects or actions with one another and to perceive some as more desirable than others. The capacity for abstraction

requires an advanced intelligence such as it exists in humans and in them alone.

The model I am advancing here does not necessarily imply the ethical theory known as utilitarianism (or, more generally, consequentialism). According to "act consequentialism," the rightness of an action is determined by the value of its consequences, so that the morally best action in a particular situation is the one the consequences of which would have the most benefit to others. I am proposing that the morality of an action depends on our ability (1) to anticipate the consequences of our actions, and (2) to pass value judgments about such consequences. But I am not asserting that the morality of actions is exclusively measured in terms of how beneficial their consequences will be to others.

The third condition necessary for ethical behavior is the ability to choose between alternative courses of actions. Pulling the trigger can be a moral action only if you have the option not to pull it. A necessary action beyond conscious control is not a moral action: the circulation of the blood or the process of food digestion is not a moral action. Whether there is free will is a question much discussed by philosophers, and the arguments are long and involved (for example, Ruse, 2006). Here, I will advance two considerations that are commonsense evidence of the existence of free will. One is personal experience, which indicates that the possibility to choose between alternatives is genuine rather than only apparent. The second consideration is that when we confront a given situation that requires action on our part, we are able mentally to explore alternative courses of action, thereby extending the field within which we can exercise our free will.

In any case, if there were no free will, there would be no ethical behavior; morality would only be an illusion. A point to be made, however, is that free will is dependent on the existence of a well-developed intelligence, which makes it possible to explore alternative courses of action and to choose one or another in view of the anticipated consequences.

ADAPTATION OR EXAPTATION?

I will now consider explicitly two issues that are largely implicit in the previous section. I have proposed that the moral sense emerges as a necessary implication of our high intellectual powers which allow us to anticipate the consequences of our actions and evaluate such consequences. But is it the case that the moral sense may have been promoted by natural selection in itself and not only indirectly as a necessary consequence of our exalted intelligence? The question in evolutionary terms is whether the moral sense is an adaptation or, rather, an exaptation. Evolutionary biologists define exaptations as features of organisms that evolved because they served some particular function, but are later co-opted to serve a different function, which was not originally the target of natural selection. The new function may replace the older function or coexist together with it. Feathers seem to have evolved first for conserving temperature, but were later co-opted in birds for flying. The beating of the human heart is an exaptation used by doctors to diagnose the state of health, although this is not why it evolved in our ancestors. The issue at hand is whether moral behavior was directly promoted by natural selection, or rather, whether it is a consequence of our exalted intelligence, which was the target of natural selection, because it made possible the construction of tools. Art, literature, religion, and many other human cultural activities might also be seen as exaptations that came about as consequences of high intelligence and tool making.

The second issue is whether some animals, apes, or other nonhuman primates, for example, may have a moral sense, however incipient, either as directly promoted by natural selection or as a consequence of their own intelligence.

The position that I'll argue here is that the human moral sense is an exaptation, not an adaptation. The moral sense consists of *judging* certain actions as either right or wrong; not of choosing and carrying out some actions rather than others, or evaluating them with respect to their practical consequences. It seems unlikely that making moral judgments would promote the reproductive fitness of those judging an action as good or evil. Nor does it seem likely that there might be some form of incipient ethical behavior that would then be further promoted by natural selection. The three necessary conditions for there being ethical behavior are manifestations of advanced intellectual abilities.

It, indeed, rather seems that the target of natural selection was the development of the advanced intellectual capacities. This was favored by natural selection because the construction and use of tools improved the strategic position of our biped ancestors. In the account I am advancing here, once bipedalism evolved and after tool using and tool making became practical, those individuals more effective in these functions had a greater probability of biological success. The biological advantage provided by the design and use of tools persisted long enough so that intellectual abilities continued to increase, eventually yielding the eminent development of intelligence that is characteristic of *H. sapiens*.

ALTRUISM AND GROUP SELECTION

A related question is whether morality would benefit a social group within which it is practiced, and, indirectly, individuals as members of the group. This seems likely to

be the case if indeed moral judgment would influence individuals to behave in ways that increase cooperation, or benefit the welfare of the social group in some way—for example, by reducing crime or protecting private property. This brings about the issue of whether there is group selection in humans and the related issues of kin selection and inclusive fitness, which I will discuss later in this chapter.

Altruistic behavior is generally not favored within a particular animal population because mutations that favor selfish over altruistic behavior will be favored by natural selection within the population, so that selfish alleles may drive out altruistic alleles. However, it may be the case that populations with a preponderance of altruistic alleles will survive and spread better than populations consisting of selfish alleles. This would be group selection. But typically there are many more individual organisms than there are populations, and individuals are born, procreate, and die at rates much higher than populations. Thus, the rate of multiplication of selfish individuals over altruists is likely to be much higher than the rate at which altruistic populations multiply relative to predominantly selfish populations.

There is, however, an important difference between animals and humans that is relevant in this respect. Namely, the fitness advantage of selfish over altruistic behavior does not apply to humans, because humans can *understand* the benefits of altruistic behavior (to the group and indirectly to them) and thus adopt altruism and protect it, by laws or otherwise, against selfish behavior that harms the social group. As Darwin wrote in *The Descent of Man*:

> *It must not be forgotten that, although a high standard of morality gives but a slight or no advantage to each individual man and his children over the other men of the same tribe, yet that an advancement in the standard of morality and an increase in the number of well-endowed men will certainly give an immense advantage to one tribe over another.*
>
> Darwin (1871, p. 159)

The theory of sociobiology advances a ready answer to the second question raised earlier: whether morality occurs in other animals, even if only as a rudiment. The theory of kin selection, sociobiologists argue, explains altruistic behavior, to the extent that it exists in other animals as well as in humans. I will propose, however, that moral behavior properly so does not exist, even incipiently, in nonhuman animals. The reason is that the three conditions required for ethical behavior depend on an advanced intelligence—which includes the capacities for free will, abstract thought, and anticipation of the future—such as it exists in *H. sapiens* and not in any other living species. It is the case that certain animals exhibit behaviors analogous with those resulting from ethical actions in humans, such as the loyalty of dogs or the appearance of compunction when they are punished. But such behaviors are either genetically determined or elicited by training (conditioned responses). Genetic determination and not moral evaluation is also what is involved in the altruistic behavior of social insects and other animals. I will argue later that biological altruism (altruism_b) and moral altruism (altruism_m) have disparate causes: kin selection in altruism_b, regard for others in altruism_m.

The capacity for ethics is an outcome of gradual evolution, but it is an attribute that only exists when the underlying attributes (ie, the intellectual capacities) reach an advanced degree. The necessary conditions for ethical behavior only come about after the crossing of an evolutionary threshold. The approach is gradual, but the conditions only appear when a degree of intelligence is reached such that the formation of abstract concepts and the anticipation of the future are possible, even though we may not be able to determine when the threshold was crossed. Thresholds occur in other evolutionary developments—for example, in the origins of life, multicellularity, and sexual reproduction—as well as in the evolution of abstract thinking and self-awareness. Thresholds also occur in the physical world: for example, water heats gradually, but at 100°C boiling begins and the transition from liquid to gas starts suddenly. Surely, human intellectual capacities came about by gradual evolution. But when looking at the world of life as it exists today, it would seem that there is a radical breach between human intelligence and that of other animals. The rudimentary cultures that exist in chimpanzees (Whiten et al., 1999, 2005) do not imply advanced intelligence as it is required for moral behavior.

The question remains: when did morality emerge in the human lineage? Did *H. habilis* or *H. erectus* have morality? What about the Neandertals, *Homo neanderthalensis*? It is difficult to determine when in hominid evolution morality emerged. The advanced degree of rationality required for moral behavior may only have been reached at the time when creative language came about, and perhaps in dependence with the development of creative language. When creative language may have come about in human evolution is, however, a question discussed elsewhere in this book (see Chapter 33).

WHENCE MORAL CODES?

Moral behavior, I have proposed, is a biological attribute of *H. sapiens*, because it is a necessary consequence of our biological makeup, namely, our high intelligence. But moral codes, I will argue, are products not of biological evolution, but of cultural evolution.

It must first be stated that moral codes, like any other cultural systems, cannot survive for long if they are outright contrary to our biology. The norms of morality must be consistent with biological nature because ethics can only exist in human individuals and in human societies. One might therefore also expect, and it is the case, that accepted norms of morality will promote behaviors that increase the biological fitness of those who behave according to them, such as child care. But the correlation between moral norms and biological fitness is neither necessary nor indeed always the case: some moral precepts common in human societies have little or nothing to do with biological fitness and some moral precepts are contrary to fitness interest.

Before going any further, it seems worthwhile to consider briefly the proposition that the justification of the codes of morality derives from religious convictions and only from them. There is no necessary or logical connection between religious faith and moral values, although there usually is a motivational or psychological connection. Religious beliefs do explain why people accept particular ethical norms, because people are motivated to do so by their religious convictions. But in following the moral and other dictates of one's religion, one is not rationally justifying the moral norms that one accepts. It may, of course, be possible to develop such rational justification: for example, when a set of religious beliefs contains propositions about human nature and the world, from which a variety of ethical norms can be logically derived. Indeed, religious authors, including, for example, Christian theologians, do often propose to justify their ethics on rational foundations concerning human nature. But in this case, the logical justification of the ethical norms does not come from religious faith as such, but from a particular (religious) conception of the world; it is the result of philosophical analysis grounded on religious premises.

It may well be that the motivational connection between religious beliefs and ethical norms and other values is the decisive one for the religious believer. But this is true in general: most people, religious or not, accept a particular set of values for social reasons, without trying to justify them rationally by means of a theory from which the moral norms can be logically derived. They accept the values that prevail in their societies, because they have learned such norms from parents, school, or religious and other authorities. The question remains: how do moral codes come about?

The short answer is, as already stated, that moral codes are products of cultural evolution, a distinctive human mode of evolution that has surpassed the biological mode, because it is a more effective form of adaptation; it is faster than biological evolution, and it can be directed. Cultural evolution is based on cultural heredity, which is Lamarckian, rather than Mendelian, so that acquired characteristics are transmitted. Most important, cultural heredity does not depend on biological inheritance, from parents to children, but is transmitted among individuals of the same or different generations, without biological bounds. A cultural mutation, an invention (think of the laptop computer, the cell phone, or rock music), can be extended to millions and millions of individuals in less than one generation.

Darwin's Chapter 5 of *The Descent of Man* (1871) is entitled, "On the Development of the Intellectual and Moral Faculties during Primeval and Civilized Times." There, he writes:

> *There can be no doubt that a tribe including many members who, from possessing in a high degree the spirit of patriotism, fidelity, obedience, courage, and sympathy, were always ready to give aid to each other and to sacrifice themselves for the common good, would be victorious over most other tribes; and this would be natural selection. At all times throughout the world tribes have supplanted other tribes; and as morality is one element in their success, the standard of morality and the number of well-endowed men will thus everywhere tend to rise and increase. (pp. 159–160)*

Darwin is making two important assertions. First, morality may contribute to the success of some tribes over others; moral behavior amounts to natural selection in the form of group selection. Second, the standards of morality will tend to improve over human history, because the higher the standards of a tribe, the more likely the success of the tribe. This assertion depends on which standards are thought to be "higher" than others. If the higher standards are defined by their contribution to the success of the tribe, then the assertion is circular. But Darwin asserts that there are some particular standards that, in his view, would contribute to tribal success: patriotism, fidelity, obedience, courage, and sympathy.

SOCIOBIOLOGY'S ACCOUNT OF MORAL BEHAVIOR

Darwin was puzzled by the social organization and behavior of hymenopterans: bees, wasps, ants, and termites. Consider Meliponinae bees, with hundreds of species across the tropics. These stingless bees have typically single-queen colonies with hundreds to thousands of workers. The queen generally mates only once. The worker bees toil, building the hive and feeding and caring for the eggs and larvae, even though they themselves are sterile and only the queen produces progeny. Assume that in some ancestral hive, a gene arises that prompts worker bees to behave as they now do. It would seem that such a gene would not be passed on to the following generation because such worker bees do not reproduce. But such inference would be erroneous.

Meliponinae bees, like other hymenopterans, have a haplo-diploid system of reproduction. Queen bees produce two kinds of eggs: some are unfertilized and develop into males (which are therefore haploid—ie, they carry only one set of genes); others are fertilized (hence, are diploid—ie, they carry two sets of genes) and develop into worker bees and occasionally into a queen. W.D. Hamilton (1964) demonstrated that with such a reproductive system the queen's daughters share in three-quarters of their genes among them, whereas the queen's daughters and their mother share in only one-half of their genes. Hence, the worker-bee genes are more effectively propagated by workers caring for their sisters than if they would produce and care for their own daughters. Natural selection can thus explain the existence in social insects of sterile castes, which exhibit a most extreme form of apparently altruistic behavior by dedicating their life to care for the progeny of another individual, the queen.

Hamilton's discovery solved the mystery that had puzzled Darwin and had continued puzzling specialists in hymenopteran biology and other evolutionists for somewhat more than a century. In 1975, the notable ant specialist Edward O. Wilson published *Sociobiology: The New Synthesis*, a treatise appropriately considered the founding document of the new discipline of sociobiology. The last chapter of the book concerned the social organization of human societies, with the telling title "Man: From Sociobiology to Sociology," and with sections dedicated to "Culture, Ritual, and Religion" and "Ethics." The first sentence of the "Ethics" section startled many readers: "Scientists and humanists should consider together the possibility that the time has come for ethics to be removed temporarily from the hands of the philosophers and biologicized" (p. 562). Wilson (1975, 1978, 1998), like other sociobiologists (Alexander, 1979; Barash, 1977; see also Kitcher, 1985; Ruse, 2000, 2006, 2010, 2012; Sober, 1993; Sober and Wilson, 1998), sees that sociobiology may provide the key for finding a naturalistic basis for ethics.

According to Wilson (1975), "The requirement for an evolutionary approach to ethics is self-evident. It should also be clear, for example, that no single set of moral standards can be applied to all human populations, let alone all sex-age classes within each population. To impose a uniform code is therefore to create complex, intractable moral dilemmas" (p. 564). Moral pluralism is, for Wilson, "innate." It seems, therefore, that, according to Wilson, biology helps us at the very least to decide that certain moral codes (eg, all those pretending to be universally applicable) are incompatible with human nature and therefore unacceptable.

However, Wilson (1978) goes further when he writes: "Human behavior—like the deepest capacities for emotional response which drive and guide it—is the circuitous technique by which human genetic material has been and will be kept intact. *Morality has no other demonstratable ultimate function* [italics added]" (p. 167). How is one to interpret this statement? It is possible that Wilson is simply giving the reason why ethical behavior exists at all; his proposition would be that humans are prompted to evaluate morally their actions as a means to preserve their genes, their biological nature. But this proposition is, in my view, erroneous. Human beings are by nature ethical beings in the sense I have expounded: they judge morally their actions because of their innate ability for anticipating the consequences of their actions, for formulating value judgments, and for free choice. Human beings exhibit ethical behavior by nature and necessity, rather than because such behavior would help to preserve their genes or serve any other purpose.

Wilson's statement may alternatively be read as a justification of human moral codes: the function of these would be to preserve human genes. But this would entail the naturalistic fallacy[1] and, worse yet, would seem to justify a morality that most people detest. If the preservation of human genes (be those of the individual or of the species) is the purpose that moral norms serve, Spencer's

1. The "naturalistic fallacy" (Moore, 1903) consists in identifying what "is" with what "ought to be." This error was pointed out already by Hume (1740/1978):

> *In every system of morality which I have hitherto met with I have always remarked that the author proceeds for some time in the ordinary way of reasoning…when of a sudden I am surprised to find, that instead of the usual copulations of propositions, is and is not, I meet with no proposition that is not connected with an ought or ought not. This change is imperceptible; but is, however, of the last consequence. For as this ought or ought not express some new relation or affirmation, it is necessary that it should be observed and explained; and at the same time a reason should be given, for what seems altogether inconceivable, how this new relation can be a deduction from others, which are entirely different from it. (p. 469)*

The naturalistic fallacy occurs whenever inferences using the terms "ought" or "ought not" are derived from premises that do not include such terms but are rather formulated using the connections "is" or "is not." An argument cannot be logically valid unless the conclusions only contain terms that are also present in the premises. To proceed logically from that which "is" to what "ought to be," it is necessary to include a premise that justifies the transition between the two expressions. But this transition is what is at stake, and one would need a previous premise to justify the validity of the one making the transition, and so on in a regression ad infinitum. In other words, from the fact that something is the case, it does not follow that it ought to be so in the ethical sense; is and ought belong to disparate logical categories. Because evolution has proceeded in a particular way, it does not follow that course is morally right or desirable. The justification of ethical norms on biological evolution, or on any other natural process, can only be achieved by introducing value judgments, human choices that prefer one rather than other object or process. Biological nature is in itself morally neutral.

Social Darwinism would seem right; racism or even genocide could be justified as morally correct, if they were perceived as the means to preserve those genes thought to be good or desirable and to eliminate those thought to be bad or undesirable. Surely Wilson is not intending to justify racism or genocide.

I believe that what Wilson and other sociobiologists are saying is something else, something of great philosophical import that has been stated, with characteristic verve and clarity, by Michael Ruse (Ruse, 2010; Ruse and Wilson, 1985): "To be blunt, my Darwinism says that substantive morality is a kind of *illusion* [italics added], put in place by our genes, in order to make us good social cooperators." Ruse proceeds to explain why the illusion of ethics is a powerful adaptation:

> *I would add that the reason why the illusion is such a successful adaptation is that not only do we believe in substantive morality, but we also believe that substantive morality does have an objective foundation. An important part of the phenomenological experience of substantive ethics is not just that we feel that we ought to do the right and proper thing, but that we feel that we ought to do the right and proper thing because it truly is the right and proper thing.*
>
> Ruse (2010, p. 309)

The deceit perpetrated on us by our genes is complete: "There are in fact no foundations, but we believe that in some sense there are" (Ruse, 2010, p. 309).

Why do "selfish genes" move us to act altruistically and behave in ways that seem morally right? The answer comes, according to sociobiologists, from the theory of kin selection that explains the altruism of haplo-diploid insects and much more, as well as from other related theoretical constructs such as inclusive fitness and reciprocal altruism. The sociobiologist's argument concerning normative ethics is not that the norms of morality can be grounded in biological evolution but rather that evolution predisposes us to accept certain moral norms, namely, those that are consistent with the objectives of natural selection. It is because of this predisposition that human moral codes sanction patterns of behavior similar to those encountered in the social behavior of animals. According to sociobiologists, the commandment to honor one's parents, the incest taboo, the greater blame usually attributed to the wife's adultery than to the husband's, and the banning or restriction of divorce are among the numerous ethical precepts and practices that endorse behaviors that are promoted by natural selection. Sociobiologists reiterate their conviction that science and ethics belong to separate logical realms; that one may not infer what is morally right or wrong from a determination of how things are or are not in nature. They avoid the naturalistic fallacy by the drastic move of denying that ethical behavior exists as an activity with different causation than any other activities or traits simply determined by our genes. Ethical behavior is simply an expression of our genes and a direct consequence of natural selection as it adapts humans, as well as other organisms, to their environments.

ALTRUISM: BIOLOGICAL AND MORAL

Evolutionists had for years struggled to find an explanation for the apparently altruistic behavior of animals. When a predator attacks a herd of zebras, adult males attempt to protect the young in the herd instead of fleeing, even if they are not their progeny. When a prairie dog sights a coyote, it will warn other members of the colony with an alarm call, even though doing so draws attention to itself and increases its own risk. Darwin tells the story of adult baboons protecting the young.[2] Examples of altruistic behaviors of this kind can be multiplied. But to speak of animal altruism is to claim not that explicit feelings of devotion or regard are present in them, but rather that animals act for the welfare of others at their own risk just as humans are expected to do when behaving altruistically.

The problem is precisely how to justify such behaviors in terms of natural selection. Assume, for example, that in a certain species there are two alternative forms of a gene (two alleles), of which one but not the other promotes altruistic behavior. Individuals possessing the altruistic allele will risk their life for the benefit of others, whereas those possessing the nonaltruistic allele will benefit from the altruistic behavior of their partners without risking themselves. Possessors of the altruistic allele will be more likely to die or fail to reproduce, and the allele for altruism will therefore be eliminated more often than the nonaltruistic allele. Eventually, after some generations, the altruistic allele will be completely replaced by the nonaltruistic one. But then, how is it that altruistic behaviors are common in animals without the benefit of ethical motivation? The explanation comes from the theory of kin selection.

To ascertain the consequences of natural selection it is necessary to take into account a gene's effects not only on a

2. *Brehm encountered in Abyssinia a great troop of baboons who were crossing a valley: some had ascended the opposite mountain, and some were still on the valley: the latter were attacked by the dogs, but the old males immediately hurried down from the rocks, and with mouths widely opened, roared so fearfully, that the dogs precipitately retreated. They were again encouraged to the attack; but by this time all the baboons had reascended the heights, excepting a young one, about six months old, who, loudly calling for aid, climbed on a block of rock and was surrounded. Now one of the largest males, a true hero, came down again from the mountain, slowly went to the young one, coaxed him, and triumphantly led him away—the dogs being too much astonished to make an attack.* (Darwin, 1971, p. 124).

particular individual but also on all individuals possessing that gene, as in the explanation of the social organization of bees and other hymenopterans. When considering altruistic behavior, one must take into account not only the costs for the altruistic individual, but also the benefits for other possessors of the same allele. Zebras live in herds where individuals are blood relatives. This is also the case for baboon troops. A gene prompting adults to protect the defenseless young would be favored by natural selection if the benefit (in terms of saved individuals that are carriers of that gene) is greater than the cost (due to the increased risk or other costs of the protectors). An individual that lacks the altruistic gene and carries instead a nonaltruistic one will not incur a cost or risk its life, but the nonaltruistic gene is partially eradicated with the death of each defenseless relative.

It follows from this line of reasoning that the more closely related the members of a herd, troop, or animal group are, the more altruistic behavior should be present. This seems to be generally the case. Consider parental care. Parental care is most obvious in the genetic benefits it entails. Parents feed and protect their young because each child has half the genes of each parent: the genes are protecting themselves, as it were, when they prompt a parent to care for its young. That is why parental care is widespread among animals.

Sociobiologists point out that many of the moral norms commonly accepted in human societies sanction behaviors also promoted by natural selection, such as the commandment to honor one's parents and the incest taboo, as pointed out earlier in this chapter. Once again, the sociobiologist's argument is that human ethical norms are sociocultural correlates of behaviors fostered by biological evolution. Ethical norms protect such evolution-determined behaviors as well as being specified by them.

The sociobiologists' arguments, however, are misguided (Ayala, 2010). Consider altruism as an example. Altruism in the biological sense (altruism_b) is defined in terms of the population genetic consequences of a certain behavior. Altruism_b is explained by the fact that genes prompting such behavior are actually favored by natural selection (when inclusive fitness is taken into account), even though the fitness of the behaving individual is decreased. But altruism in the moral sense (altruism_m) is explained in terms of motivations: a person chooses to risk his or her own life (or incur some cost) for the benefit of somebody else. The similarity between altruism_b and altruism_m is only with respect to the consequences: an individual's chances are improved by the behavior of another individual who incurs a risk or cost. The underlying causations are completely disparate: the ensuing genetic benefits in altruism_b; regard for others in altruism_m. As Darwin put it, the altruistic behavior of a baboon and a human are similar in that they both benefit other individuals, but they differ in that humans carry out an assessment, which baboons do not. Humans make moral judgments as a necessary consequence of their eminent intellectual abilities. Their judgments, as well as the moral norms on which they are based, are not always accompanied by biological gain.

Parental care is a behavior generally favored by natural selection, which may also be present in virtually all codes of morality, from primitive to more advanced societies. There are other human behaviors sanctioned by moral norms that have biological correlates favored by natural selection. One example is monogamy, which occurs in some animal species but not in many others. It is also sanctioned in many human cultures, but surely not in all. Polygamy is accepted in some current human cultures and surely was more so in the past. Food sharing outside the mother–offspring unit rarely occurs in primates, with the exception of chimpanzees and capuchin monkeys, although even in chimpanzees, food sharing is highly selective and often associated with reciprocity. A more common form of mutual aid among primates is coalition formation; alliances are formed in fighting other conspecifics, although these alliances are labile, with partners readily changing partners.

One interesting behavior, associated with a sense of justice, or equal pay for equal work, has been described by Sarah Brosnan and Frans de Waal (2003; see also de Waal, 1996) in the brown capuchin monkey, *Cebus paella*. Monkeys responded negatively to unequal rewards in exchanges with a human experimenter. Monkeys refused to participate in an exchange when they witnessed that a conspecific had obtained a more attractive reward for equal effort.

Is the capuchin behavior phylogenetically related to the human virtue of justice? This seems unlikely, since similar behavioral patterns have not been observed in other primates, including apes, phylogenetically closer to humans. Moreover, it was later shown that capuchin monkeys reject a food reward when a more attractive reward is visible to the monkeys, whether this more attractive reward is offered to other monkeys or is simply present within their sight. Cannibalism is practiced by chimps, as well as by human cultures of the past. Do we have a phylogenetically acquired predisposition to cannibalism as a morally acceptable behavior? This seems unlikely. Moral codes arise in human societies by cultural evolution. The moral codes that lead to successful societies tend to be widespread.

Since time immemorial, human societies have experimented with moral systems. Some have succeeded and spread widely through humankind, like the Ten Commandments, although other moral systems persist in different human societies. Many moral systems of the past have surely become extinct because they were replaced or because the societies that held them became extinct.

The moral systems that currently prevail in humankind are those that were favored by cultural evolution. They were propagated within particular societies for reasons that might be difficult to fathom, but that surely must have included the perception by individuals that a particular moral system was beneficial for them, at least to the extent that it was beneficial for their society by promoting social stability and success. Acceptance of some precepts in many societies is reinforced by civil authority (eg, those who kill or commit adultery will be punished) and by religious beliefs (God is watching and you'll go to hell if you misbehave). Religious, legal, and political systems, as well as belief systems, are themselves outcomes of cultural evolution.

GENE–CULTURE COEVOLUTION

A different explanation of the evolution of the moral sense has been advanced by proponents of the theory of gene–culture coevolution (Richerson and Boyd, 2005; Strimling et al., 2009; Richerson et al., 2010; see also Greene et al., 2001; Haidt, 2007). It is assumed that cultural variation among tribes in patriotism, fidelity, sympathy, and other moralizing behaviors may have occurred incipiently in early hominid populations, starting at least with *H. habilis*. This cultural variation may have, in turn, selected for genes that endowed early humans with primitive moral emotions. Primitive moral emotions would in turn have facilitated the evolution of more advanced cultural codes of morality. Repeated rounds of gene–cultural coevolution would have gradually increased both the moral sense itself and the systems of moral norms. That is, the evolution of morality would have been directly promoted by natural selection in a process where the moral sense and the moral norms would have coevolved.

The gene–culture coevolution account of the evolution of morality is, of course, radically different from the theory I have advanced earlier in this chapter, in which moral behavior evolved not because it increased fitness, but as a consequence of advanced intelligence, which allowed humans to see the benefits that adherence to moral norms bring to society and to its members. The extreme variation in moral codes among recent human populations and the rapid evolution of moral norms over short time spans (see later in this chapter) would seem to favor the explanation I have proposed. Gene–culture coevolution would rather lead to a more nearly universal system of morality, which would have come about gradually as our hominin ancestors gradually evolved toward becoming *H. sapiens*.

Empathy, or the predisposition to mentally assimilate the feelings of other individuals, has recently been extensively discussed in the context of altruistic or moral behavior. Incipient forms of empathy seem to be present in other animals. In humans, increasing evidence indicates that we automatically simulate the experiences of other humans (Gazzaniga, 2005, pp. 158–199, 2008). Empathy is a common human phenomenon, surely associated with our advanced intelligence, which allows us to understand the harms or benefits that affect other humans, as well as their associated feelings. Empathic humans may consequently choose to behave according to how their behavior will impact those for whom we feel empathy. That is, human empathy occurs because of our advanced intelligence. Humans may choose to behave altruistically, or not, that is, morally or not, in terms of the anticipated consequences of their actions to others.

The question remains, when did morality emerge in the human lineage? Did *H. habilis* or *H. erectus* have morality? What about the Neandertals, *H. neanderthalensis*? When in hominid evolution morality emerged is difficult to determine. As pointed out earlier, the capacity for ethics is an outcome of gradual evolution, but it only comes about when the underlying attributes (ie, the intellectual capacities) reach an advanced degree. When in human evolutionary history this threshold was reached would seem impossible to determine, at least at the current state of knowledge.

One additional observation is that the norms of morality, as they exist in any particular culture, are felt to be universal within that culture. Yet, similarly as other elements of culture, they are continuously evolving, often within a single generation. As Steven Pinker has pointed out, western societies have recently experienced the moralization and amoralization of diverse behaviors. Thus, "smoking has become moralized…now treated as immoral…At the same time many behaviors have become amoralized, switched from moral failings to lifestyle choices. They include divorce, illegitimacy, working mothers, marijuana use and homosexuality" (Pinker, 2002, p. 34). Acceptance by individuals or groups of particular sets of moral norms is often reinforced by civil authority (eg, those who kill or commit adultery will be punished) and by religious beliefs (God is watching and you'll go to hell if you misbehave). But it is worth noticing that the legal and political systems that govern human societies, as well as the belief systems held by religion, are themselves outcomes of cultural evolution, as it has eventuated over human history, particularly over the last few millennia.

AESTHETICS

Aesthetics is a term forged by Alexander Gottlieb Baumgarten (1714–1762) to refer to a philosophy of taste and beauty, but the appreciation of beauty transcends the German Enlightenment. Indeed, the capacity for appreciating beauty, the aesthetic qualities of objects, motions, and sounds is a human universal; all human groups possess this

competence. The capacity for producing aesthetic items is also universal: sculptors, painters, dancers, and musicians are pervasive in all human cultures and historical epochs. However, *appreciating* aesthetic attributes goes beyond producing them in two respects. First, artists or producers of beauty make up a small fraction of individuals in human groups; on the contrary spectators are numerous. This difference becomes, nevertheless, reduced, or even eliminated, if we extend the production of beauty beyond those who might be considered professional artists to the decoration or furniture of a home, the preparation and presentation of food for a meal, and singing or dancing in the course of ordinary life. A second difference is that it is possible to appreciate aesthetic qualities in natural objects and events, such as a sunset or sunrise, a snow covered mountain, a forest, or bird songs (Cela-Conde and Ayala, 2007).

An important difference between ethics and aesthetics is that ethical values are considered, by and large, objective, while aesthetic values are considered much more subjective. Individuals within a given culture, and largely across cultures, usually agree about what is necessarily wrong and what is absolutely right, while qualifying an object or song as beautiful tolerates considerably more diversity of opinion: *de gustibus non est disputandum* (Benardini, 2015).

It does not seem possible to determine the phylogenetic origin of the human capacity for appreciating beauty. Neither fossil nor archaeological records provide convincing evidence to ascertain the appearance of this competence. It is not possible to determine whether spectators with the ability to appreciate landscapes, motions, or songs existed in previous human species, or when in the evolution of *H. sapiens* or *H. neanderthalensis* the capacity to appreciate beauty came about. It seems that the best we might be able to do is to determine when human artisans first started to produce objects or activities with aesthetic qualities, and conclude that the appreciation of beauty would already be present among their human partners.

Ascertaining when the production of objects with aesthetic attributes first came about in human evolution is less elusive than ascertaining when the appreciation of beauty first appeared, but even so it is far from obvious. The Paleolithic polychromies representing bison and horses in the caves of Altamira or Lascaux are doubtless art works, but what about the bifacial symmetric hand axes made by *H. erectus* 1 Ma and earlier, and even the first recognizable stone tools produced by *H. habilis* as early as 2.5 Ma? We'll first explore the production of objects doubtless produced to serve useful purposes, such as hand axes, and leave unanswered for the very early of such useful objects whether aesthetic considerations may have played a role in their design.

The start of the Paleolithic, or "Old Stone Age," is defined precisely by the appearance of the first stone tools, around 2.6 Ma, associated in turn with *H. habilis*, which is the first species of *Homo*, named *habilis*, precisely for their ability, first in human evolution, to construct tools. The Paleolithic lasted until the Neolithic 12−10 ka, the "Modern Stone Age" or Holocene that lasted until about 2000 years BCE, when modern history starts.

Paleolithic history is often recognized by a succession of stages or cultures, characterized by distinct tools and other products of human activity and named after localities where the characteristic human objects were found. Successively, these cultures are known as Oldowan (named after the Olduvai site in Tanzania), from about 2.5 Ma until about 1.5 Ma; Acheulan (named after the St. Acheul site in France), from about 1.5 Ma until 150−120 ka, encompassing African and European *H. erectus* and archaic *H. sapiens*; Mousterian, 150−120 ka until about 40 ka, with *H. neanderthalensis* and *H. sapiens* in Europe; succeeded by the Aurignacian culture, lasting from about 40 to about 18 ka, during which clearly defined artistic expressions appear as decorations on cave walls; and then the Magdalenian, with the highest artistic expression of the Paleolithic, from 18 to 10 ka, coinciding with the peak of the Würm glaciation, the last one and most severe impacting our planet. The last three cultures are designated after the French sites of Le Moustier, Aurignac, and La Magdalene.

OLDOWAN AND ACHEULEAN CULTURES

Olduvai Gorge (Tanzania) has been a source of numerous hominin fossils since the middle of the 20th century. Although Olduvai Gorge is not the first place in which stone tools were found, it gave name to the earliest known lithic industry: Oldowan culture. A lithic industry can be described as a set of diverse stones manipulated by hominins to obtain tools to cut, scrape, or hit. They are diverse tools obtained by hitting pebbles of different hard materials. Silex, quartz, flint, granite, and basalt are some of the materials used for tool making. In the Oldowan culture, the size of the round-shaped cores is variable, but they usually fit comfortably in the hand; they are tennis ball−sized stones. Many tools belonging to different traditions fit within these generic characteristics. What specifically identifies Oldowan culture is that its tools are obtained with very few knocks, sometimes only one. The resultant tools are misleadingly crude in appearance, although it is not easy to hit the stones with enough precision to obtain cutting edges and efficient flakes (Fig. 35.1).

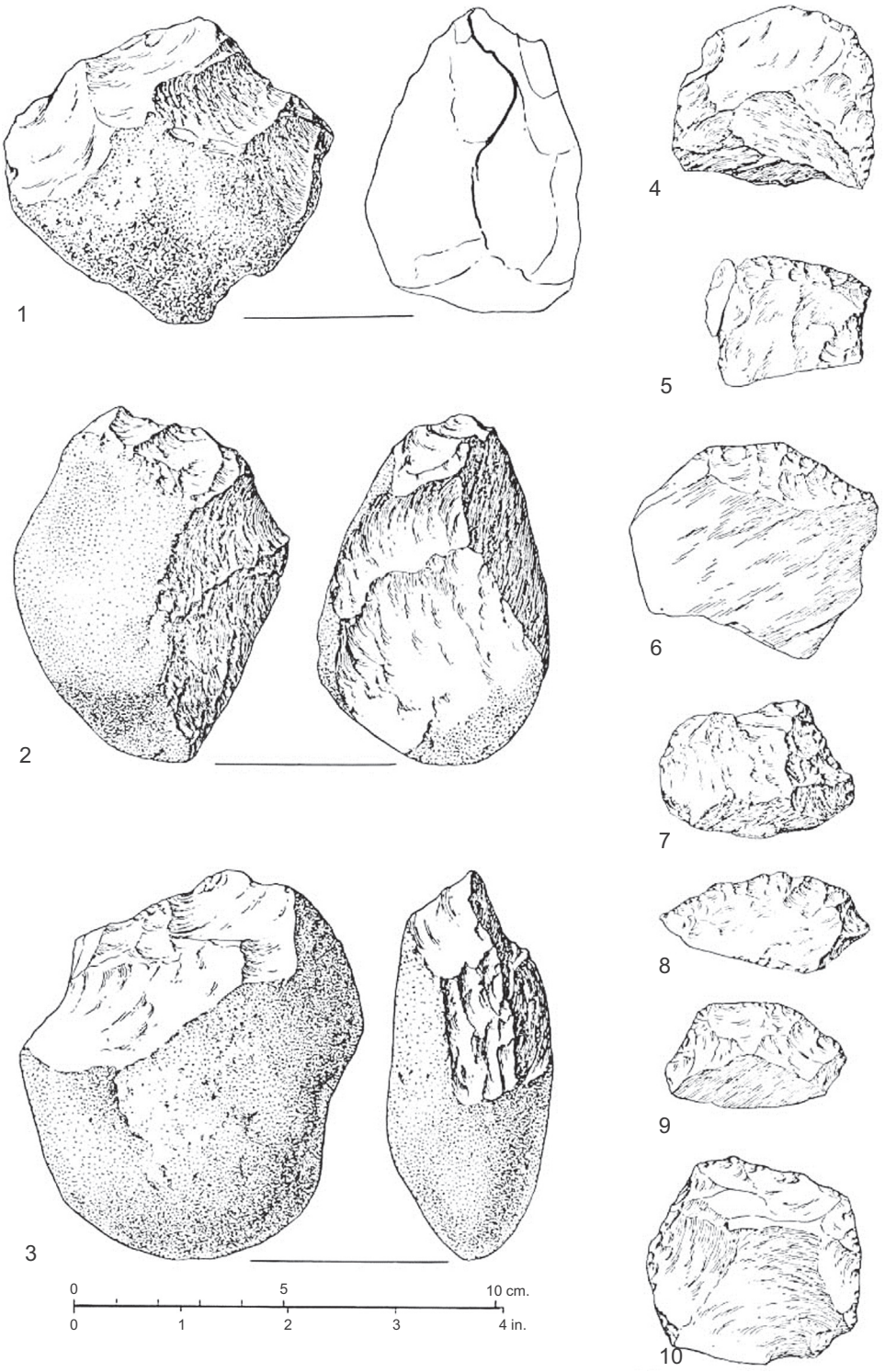

FIGURE 35.1 Oldowan tools. 1−3: Lava choppers; 4−10, quarcite flakes. *Drawing by Leakey, M.D., 1971. Olduvai Gorge 3. Excavations in Beds I and II 1960−1963. Cambridge University Press, Cambridge.*

The idea we have of their function depends on the way we interpret the adaptation of hominins that used them. The most important tools would be the hand axes that allow hitting a cranium or femur hard enough to break it. But for butchering almost whole animals, flakes would be the essential tools.

The Oldowan culture was not restricted to Olduvai. Stone tools have also been found at Kenyan and Ethiopian sites, some older than Olduvai, such as Gona in the Middle Awash region (Ethiopia), where some findings extend back to 2.6−2.5 Ma. Other Ethiopian sites include Hadar and Ono and, just south of them but already in Kenya, the Lokalalei site in West Turkana, sites dated 2.0−2.3 Ma, which collectively have yielded thousands of stone tools. The dates for these sites are compatible with the attribution of their stone tools to *H. habilis*. The oldest *H. habilis* fossils from the Afar region in Ethiopia have been dated between 2.75 and 2.80 Ma (Villmoare et al., 2015; DiMaggio et al., 2015).

The issue arises as to what sort of knowledge was possessed by the *H. habilis* hominins who produced these stone tools. There can be little doubt that they had acquired some capacity for abstract knowledge and for forming images of realities not present, manifest in the construction of tools that would be used at a later time, for purposes not immediately present. However, the tools were crude, showing no evidence of any aesthetic intention (Fig. 35.2). This would change later, during the ensuing Acheulan culture, where symmetric, carefully designed hand axes were produced that betray an appreciation of beauty. Their creators were other, more developed hominin species, which include *H. erectus*, *H. neanderthalensis* and, perhaps, archaic *H. sapiens*.

FIGURE 35.2 Flake production by the Oldowan technique. *Picture from Plummer, T., 2004. Flaked stones and old bones: biological and cultural evolution at the dawn of technology. Yearbook of Physical Anthropology 47, 118−164.*

The transition, described by Mary Leakey (1975), from Oldowan tools to a different and more advanced industry, the Acheulean culture, can be observed in Olduvai. Acheulean tools made with great care were identified for the first time at the St. Acheul site (France). Acheulean culture appeared in East Africa slightly over 1.5 Ma, and extended to the rest of the Old World to a greater or lesser degree until around 0.3 Ma. Its most characteristic element is the biface, "teardrop shaped in outline, biconvex in cross-section, and commonly manufactured on large (more than 10 cm) unifacially or bifacially flaked cobbles, flakes, and slabs" (Noll and Petraglia, 2003). But the term biface corresponds to a form of manufacture rather than to a tool. Bifaces led to different utensils, such as those shown in Fig. 35.3.

Mary Leakey (1975) described the transition from Oldowan culture to Acheulean culture as gradual. Subsequent studies, as argued by Isaac (1969) have convincingly shown that the improvement of the necessary techniques to go from the Oldowan to the Acheulean traditions could not have taken place gradually. A completely new type of manipulation would have appeared with Acheulean culture, a true change in the way of carrying out the operations involved in tool making.

The cultural sequence identified by Mary Leakey (1975) involved a three-stage transition (Table 35.1): first, the evolution of progressively more sophisticated techniques within the Oldowan culture itself; second, the coexistence of Oldowan and Acheulean tools; and third, the disappearance of the former, and further development of Acheulean techniques. Isaac (1969) described that sequence in terms of four cultural-stratigraphical associations, from the oldest to the youngest, as Oldowan, developed Oldowan, lower Acheulean, and upper Acheulean.

To what extent can the Acheulean tradition be considered a continuation or a rupture regarding Oldowan? Was developed Oldowan a transition phase toward subsequent cultures? The required technique to execute the Acheulean bifaces is different from Oldowan in several features. The first difference is the succession of strikes required to produce a hand axe, which contrasts with the few and unorganized strikes required to manufacture a protobiface. The production of very long oval flakes (more than 10 cm), characteristic of Acheulean techniques, is its key difference from the advanced Oldowan traditions. The shape of those long flakes is not very different from the bifaces themselves. This is why Isaac (1969) suggested that they could be transformed into hand axes without too much effort.

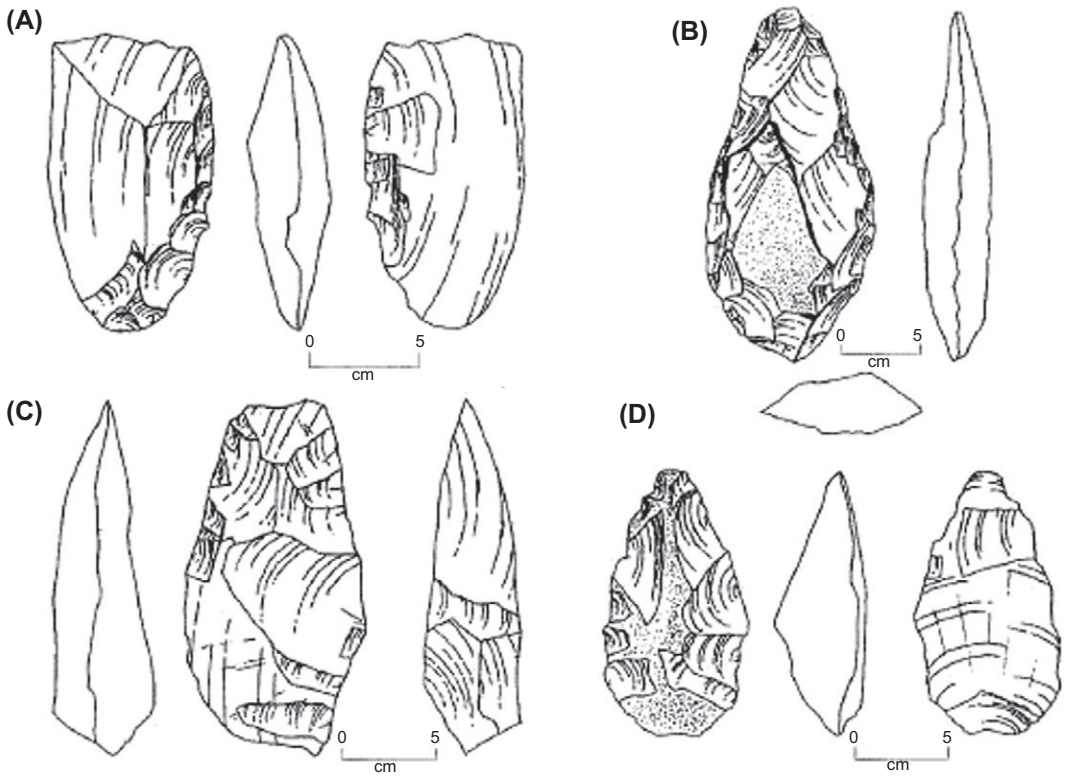

FIGURE 35.3 Bifaces destined to different uses. (A) cleaver; (B) hand axe; (C) knife; and (D) pick. *From Noll, M.P., Petraglia, M.D., 2003. Acheulean bifaces and early human behavioral patterns in East Africa and south India. In: Soressi M., Dibble, H.L. (Eds.), Multiple Approaches to the Study of Bifacial Technologies. University of Pennsylvania Museum of Archaeology and Anthropology, Philadelphia, pp. 31–53.*

TABLE 35.1 Cultural Sequence at Olduvai Established by Mary Leakey (1975, Modified)

Beds	Age in Ma	Number of Pieces	Industries
Masek	0.2	187	Acheulean
IV	0.7–0.2	686	Acheulean
		979	Developed Oldowan C
Middle part of III	1.5–0.7	99	Acheulean
Middle part of II	1.7–1.5	683	Developed Oldowan A
I and lower part of II	1.9–1.7	537	Oldowan

The appearance of the technique for producing flakes suddenly changed the possibilities for tool manufacture.

Given that the production of those flakes involves starting from large cores, the availability of quarries with such raw materials can determine important differences in the cultural content of different sites. The manipulation of large blocks of material (mostly lava and quartzite) to produce long flakes seems to have been the turning point for the development of the Acheulean culture. It would also have involved risk for those who had to manipulate stones of large size (Schick and Toth, 1993).

The most advanced Acheulean stage includes hand axes with such symmetrical and carefully elaborated edges that they must have required the so-called soft-hammer technique (Fig. 35.4), which uses softer hammers than the cores themselves, such as wood or bone. Knapping with such a tool allowed more precise control and certainly required more time. Schick and Toth (1993) have provided a detailed description of the process.

Three events are usually considered to have taken place together during the evolution of early- and middle-Pleistocene hominins: the appearance of *H. erectus*, Acheulean culture, and the first migration of hominins out of the African continent. The usual interpretation suggests that these three events are related. Leaving Africa confronted hominins with climates colder than the Rift's. Adaptation to those extreme conditions was made possible by cultural novelties, such as the control of fire. The adaptation was achieved by *erectus*-grade hominins, associated with Acheulean culture.

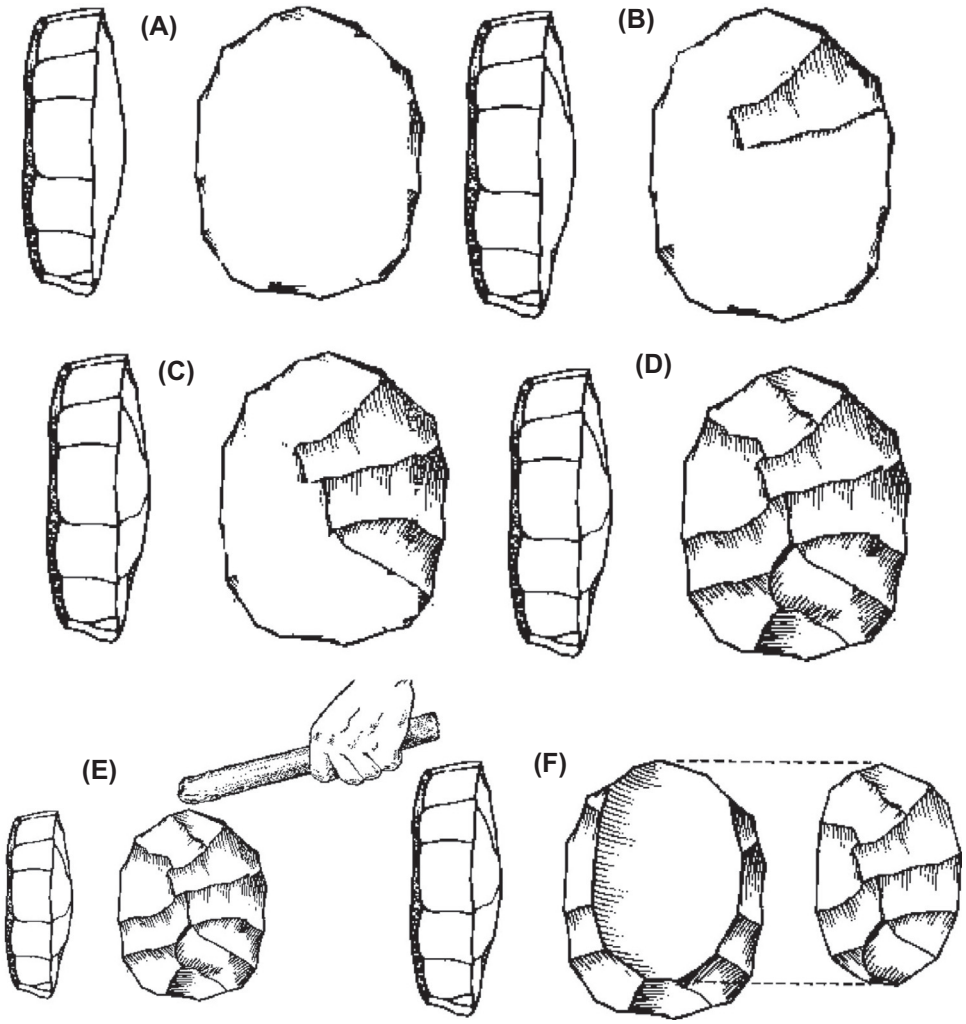

FIGURE 35.4 Levallois technique. Phases in the construction of a tool by flake removal. (A) Preparation of an adequately shaped core; (B) and (C) removal of flakes; (D) the prepared platform is obtained; (E) a last blow with a soft hammer separates the tool from the core (F). *Drawings from http://www.hf.uio.no/iakh/forskning/sarc/iakh/lithic/LEV/Lev.htm.*

The central element of Acheulean culture, the hand axe, is absent in many early European sites with signs of human presence (Italy, France, Germany, Czech Republic, and Spain). It was not until a second colonizing wave, which took place about half a million years ago, that Acheulean hand axes were introduced. Sites corresponding to this time interval include Torralba and Ambrona (Spain); St. Acheul and Abbeville (France); Swanscombe, Boxgrove, and Hoxne (England); and Torre di Pietra and Venosa-Notarchirico (Italy).

MOUSTERIAN CULTURE AND NEANDERTALS

Mousterian culture (c. 100–40 ka) is the lithic tool tradition that evolved from Acheulean culture during the middle Paleolithic. It was followed by the Aurignacian technical and artistic explosion (40–18 ka), with tools and decorated objects that contrast sharply with the Mousterian and earlier cultures. Mousterian culture includes controversial features, including objects clearly created with a decorative intention. Participants were *H. neanderthalensis*, as well as modern *H. sapiens*.

Mousterian tool-making techniques produced tools that were much more specialized than Acheulean ones; the Mousterian tools were given a form before sharpening their edges. The most typical Mousterian tools found in Europe and the Near East are flakes produced by means of the Levallois technique, which were subsequently modified to produce diverse and shaper edges. Objects made from bone are less frequent, but up to 60 types of flake and stone foil can be identified, which served different functions (Bordes, 1979).

The Levallois technique appeared during the Acheulean period, and was used thereafter. Its pinnacle was reached during the Mousterian culture. This technique produces

flakes or foils with a very precise shape from stone cores that serve as raw material. The cores must first be carefully prepared by trimming their edges, removing small flakes until the core has the correct shape. Thereafter, with the last blow, the desired flake, a Levallois point for instance, is obtained (Fig. 35.4). The final results of the process, which include points, scrapers, among many other instruments, are subsequently modified to sharpen their edges. The amazing care with which the material was worked constitutes, according to Bordes (1953), evidence that these tools were intended to last for a long time in a permanent living location. They also seem to reflect an aesthetic intention. Tools obtained by means of the Levallois technique are typical of European and Near-East Mousterian sites.

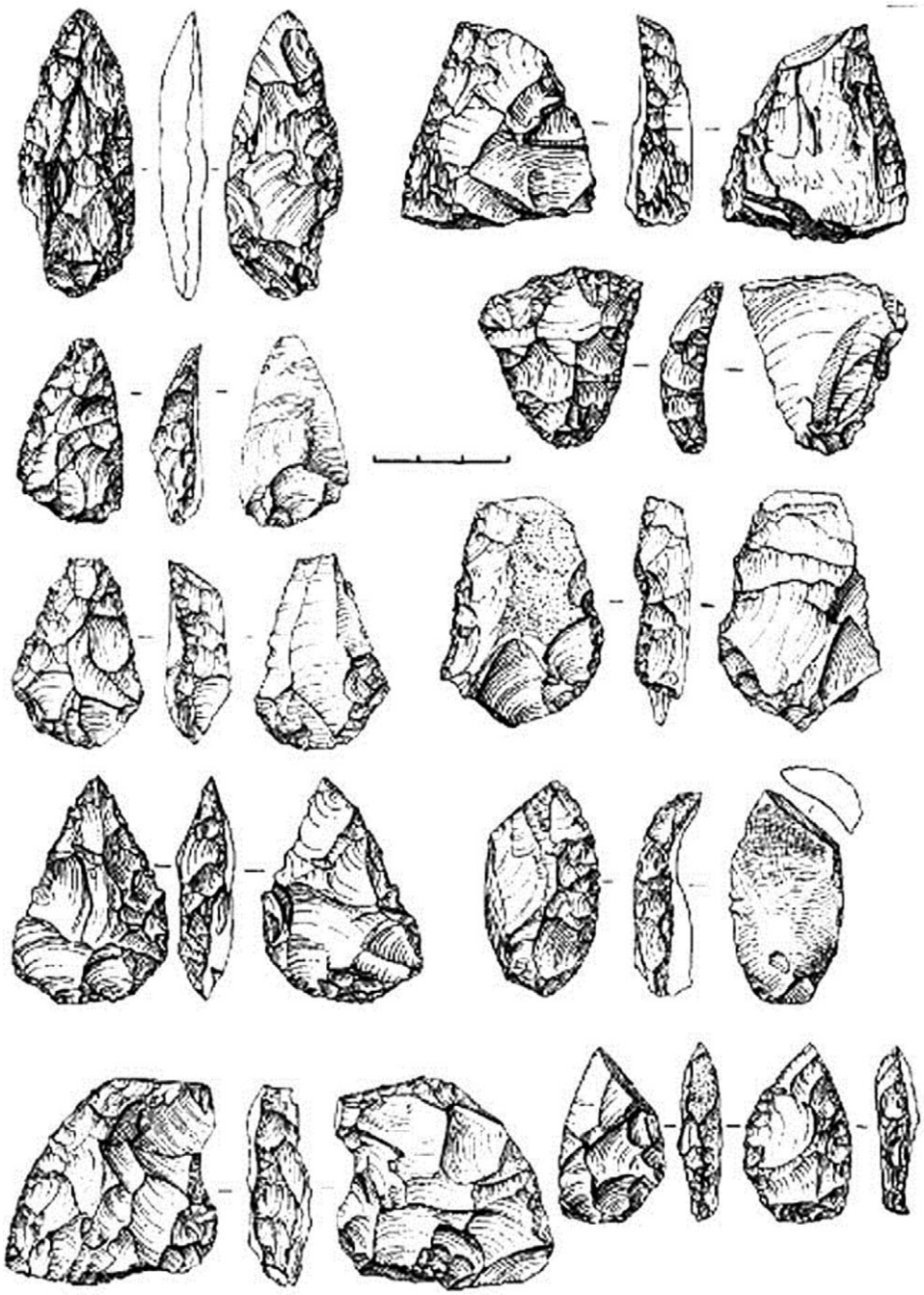

FIGURE 35.5 Mousterian hand axes from Mezmaiskaya Cave (Caucasus). *Figure from Doronichev, V., Golovanova, L., 2003. Bifacial tools in the lower and middle Paleolithic of the Caucasus and their contexts. In: Soressi, M., Dibble, H.L. (Eds.), Multiple Approaches to the Study of Bifacial Technologies. Museum of Archaelogy and Anthropology. Philadelphia, PA, pp. 77–107.*

Bifaces, on the contrary—so abundant in Acheulean sites—are scarce. The difference has to do mostly with the manipulation of the tools; scrapers were already produced using Acheulean, and even Oldowan, techniques.

Most European and Near-East sites belonging to the Würm glacial period contain Mousterian tools (named after the Le Moustier site, Dordogne, France). The archaeological richness and sedimentary breadth of some of these sites, like La Ferrassie, La Quina, and Combe-Grenal, grants them a special interest for studying the interaction between cultural utensils and adaptive responses. Similar Mousterian utensils have appeared in the Near East, at Tabun, Skuhl, and Qafzeh.

The identification between the Mousterian culture and *H. neanderthalensis* has been considered so consistent that, repeatedly, European sites yielding no human specimens, or with scarce and fragmented remains, were attributed to Neandertals on the sole basis of the presence of Mousterian utensils. Despite the difficulties inherent in associating a given species with a cultural tradition, it was thought to be beyond a doubt that Mousterian culture was part of the Neandertal identity. Scrapers and Levallois points, which were very similar to the typical European ones, turned up also in Near-East sites (Bar-Yosef and Vandermeersch, 1993). Neandertals also lived there, of course (Fig. 35.5), but in contrast with European sites, a distinction could not be drawn between localities that had housed Neandertals and anatomically modern humans solely on the grounds of the cultural traditions. The more or less systematic distinction between Neandertal—Mousterian and Cro-Magnon—Châtelperronian (or Aurignacian, or Magdalenian) helped to clarify the situation in Europe. But it could not be transferred to the Near East, where sites occupied by Neandertals and those inhabited by anatomically modern humans, proto-Cro-Magnons, yielded the same utensils of the Mousterian tradition.

This implies several things. First, that cultural sharing was common during the middle Paleolithic, at least in Levant sites. Second, that during the initial stages of their occupation of the eastern shore of the Mediterranean, anatomically modern humans made use of the same utensils as Neandertals. Hence, it seems that, at the time, there was no technical superiority of modern humans over Neandertals. The third and most important implication has to do with the inferences that can be made because Neandertals and *H. sapiens* shared identical tool-making techniques. The production of Mousterian tools required complex mental capabilities. Were Neandertal cognitive abilities as complex as those currently characteristic of our own species? Some authors have argued in favor of high cognitive capacities in Neandertals, arguing that other kinds of items were, indeed, indications of Neandertal aesthetic, religious, symbolic, and even maybe linguistic, capacities. Numerous Neandertal burials can be interpreted as a functional response to the need of disposing of the bodies, even if only for hygienic reasons. But they could also be understood as the reflection of transcendent thinking, beyond the simple human motivation of preserving the bodies of deceased loved ones, probably reflecting symbolic and even religious intentions.

A possible key to the symbolic thought of *H. neanderthalensis* could come from stone and bone objects belonging to the Mousterian tradition. Making tools to use them in one way or another requires a capacity to formulate objectives and anticipate behaviors. Beyond their utility, Acheulean hand axes are beautiful objects (Fig. 35.6). Were these tools created with the intention of being beautiful? Bifaces could be an early manifestation of the evolution of preferences for lateral symmetry. It is true that the Acheulean symmetrical tools and, more so, Mousterian tools turned into beautiful objects, artistic representations for us, who live hundreds of thousands of years after the objects were manufactured. But were they also so perceived, at least to some extent, by those who manufactured them? Can a gradual and slow evolution

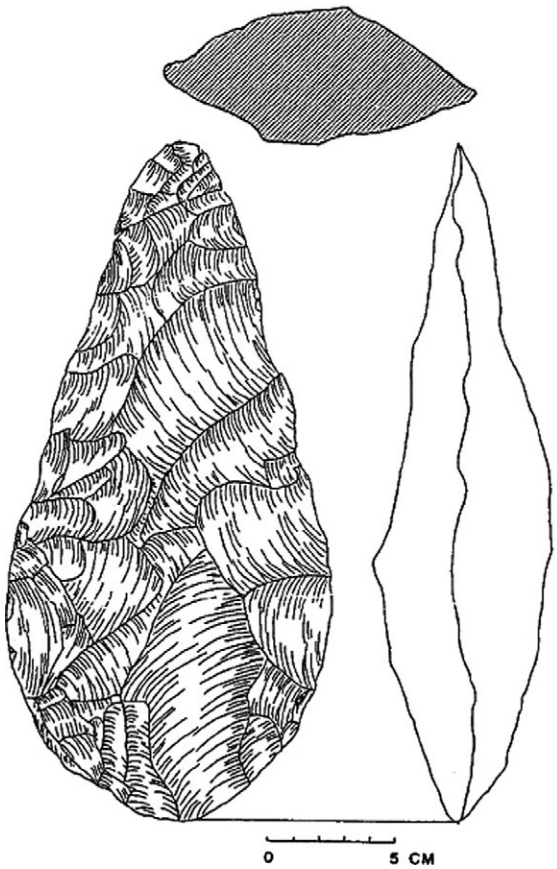

FIGURE 35.6 Hand axe from Isimila (Tanzania, c.300,000 year). As Tomas Wynn observed, this artifact has congruent symmetry in three dimensions. *Illustration from Wynn, T., 2002. Archaeology and cognitive evolution. Behavioral and Brain Sciences 25, 389–402.*

toward more advanced symbolic objects be documented? Or, rather, did symbolic expression and perception come about relatively suddenly, late in human evolution?

SYMBOLISM AND AESTHETICS: AURIGNACIAN AND MAGDALENIAN CULTURES

The symmetry of Acheulean hand axes could be considered as a possible indication of symbolism. The earliest of these tools are about 1.5 million years old (Leakey, 1975). Realistic representations, such as the Altamira, Lascaux, Chauvet, and other cave paintings from Spain and France were made toward the end of the upper Pleistocene, about 14,000 years ago. There is an enormous time gap between these two cultural manifestations (symmetry and realistic painting). Within this gap, there is the Mousterian culture, described earlier, characteristic of the European middle Paleolithic, ranging from about 100,000 to 40,000 years ago. The ensuing Aurignacian (c. 40−18 ka) and the Magdalenian (c. 18−10 ka) cultures include drawings, engravings, and paintings with unquestionable intentional aesthetic and symbolic characteristics, much beyond the symbolism and beauty that might be attributed to the Mousterian and earlier cultures.

There are two mutually exclusive hypotheses about the process that led to the massive production of artistic representations unquestionably charged with symbolism: the gradual and explosive models. The former argues that the capacity to appreciate Acheulean beautiful forms evolved gradually and continuously, leading to the great abundance of late-Paleolithic artistic objects. This gradual model does not refer to an origin of art. This origin is thought to be fuzzy, widespread in space and continuous in time. According to this model, the initial manifestations of that origin were scarce; slowly, over a long period of time, they became progressively generalized. On the contrary, the explosive model of the appearance of the symbolism characteristic of art argues that it appeared fairly suddenly during the late Paleolithic, and that it is exclusively an attribute of modern humans. The great cognitive transformation evinced in the upper-Paleolithic artistic explosion must have included different capacities for adaptation in our ancestors. Several authors have suggested coevolutionary sequences of cultural manufactures and communicative abilities. Some of these models (Davidson and Noble, 1989) have put forward the hypothesis that relates the origin of art itself, and not just the general cultural sequence, with the origin of language. They believe that drawing requires prior communication. Drawing later transformed communication into language. Davidson and Noble (1989) argue that pictorial representations are halfway between reality and language. There are plenty of hypothetical speculations and models of the evolution of language, but this is a matter that will not be pursued here (see Chapter 33 in this book.)

The appearance of cave art since early in the Aurignacian period and culminating during the Magdalenian, seems "explosive" from our distance of several thousand years. An extensive monograph by the distinguished painter and muralist Joaquín Vaquero Turcios (1995) provides detailed historical and artistic analysis of cave art, particularly wall paintings. He has identified 72 caves, distributed into eight regions in Northern Spain and Southern France (Fig. 35.7). Best known are Altamira and El Castillo in region 2 (Cantabria, Spain), Lascaux in region 5 (Dordogne-Gironde, France), and Chauvet in region 8 (Ardèche, France). All the caves seem to have experienced two distinct periods of artistic activity, the first around 40−34 ka and the second around 18−14 ka. Why these two periods of activity and why at relatively similar

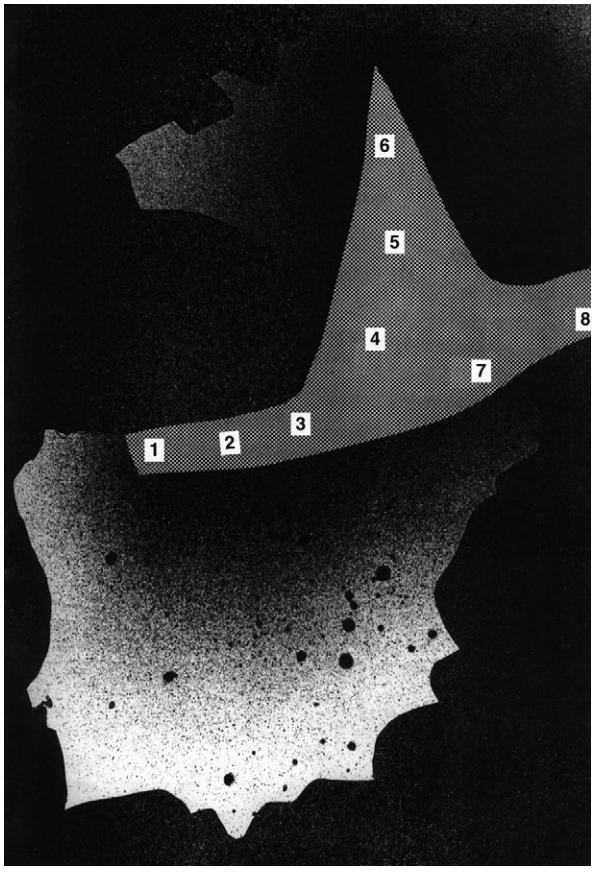

FIGURE 35.7 The seven central regions of Paleolithic cave art: (1) Asturias; (2) Cantabria; (3) País Vasco; (4) Dordogne (Lot and Tarn); (5) Dordogne (Gironde); (6) Dordogne (Charente and Yonne); (7) Aragon and Estern Pyrenees; (8) Garde, Ardèche, Ain. The caves of Altamira and El Castillo are in region 2; Lascaux is in region 5; Chauvet is in region 8. *After Vaquero Turcios, J., 1995. Maestros Subterráneos. Celeste Ediciones, S.A., Madrid, p. 21.*

times in all caves is not known. One consideration is the overlap with the Würm glaciation, which reached its climax around 16 ka. Caves may have served as occasional refuge, as well as places for social, and perhaps religious, interaction.

One footnote that deserves attention is illumination. How did the artists, as well as visitors over many years, manage to have light in the depth of caves, often hundreds of feet from the cave entrance, where no sunlight or any conceivable form of natural light could reach? Wax and various fats were the most common forms of lighting before modern times. But most fat or wax candles produce smoke that would have made it all but impossible to paint or to draw, and visitors would have obliterated with their smoke any paintings decorating the walls. Vaquero Turcios (1995) discovered that bone marrow, particularly from the calves of cattle and other large mammals, burns without producing smoke. Small handheld stones covered with lumps of bone marrow and with an ignited wick could provide lighting for hours at a time (Fig. 35.8). The fire was started by rubbing stones or wood sticks against each other. Vaquero Turcios (1995) has shown how the artists changing their position around a particular spot could suitably illuminate it, and at times provide vantage points for identifying irregularities on the walls that could be used to represent different animal forms.

The Aurignacian cave paintings are mostly red ochre stencils of human hands and dot alignments with different configurations and difficult-to-ascertain symbolism; sometimes the hand stencils and the dots are associated on the same wall with sketched and often incomplete animal designs, some of which may have been added later, during the Magdalenian period (Fig. 35.9). The Magdalenian paintings of the great "cave Sistine chapels," particularly those of Altamira (Figs. 35.10 and 35.11), Chauvet, and Lascaux are polychrome paintings of superb artistic value, even though their symbolism beyond their decorative value remains obscure. Some may have served conjuring, magic, or even religious purposes.

FIGURE 35.9 Fragment of the "Panel of the Hands," on the ceiling of a low cavern in El Castillo. The hand stencils start near the floor; the incomplete bison would have been added later. *After Vaquero Turcios, J., 1995. Maestros Subterráneos. Celeste Ediciones, S.A., Madrid, p. 105.*

FIGURE 35.8 A fire lamp. Over the stone, lumps of bone marrow (nearly exhausted) and the protruding wick. *After Vaquero Turcios, J., 1995. Maestros Subterráneos. Celeste Ediciones, S.A., Madrid, p. 25.*

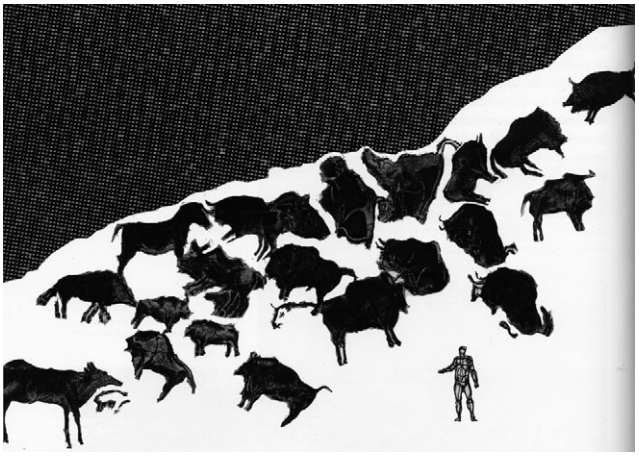

FIGURE 35.10 Drawing in black and white of the ceiling of one of the main caverns in Altamira. The bison, horses, deer, and boar are painted in vivid colors, with prevailing red ochre. Approximate sizing is provided by the added drawing of the artist himself. *After Vaquero Turcios, J., 1995. Maestros Subterráneos. Celeste Ediciones, S.A., Madrid, p. 140.*

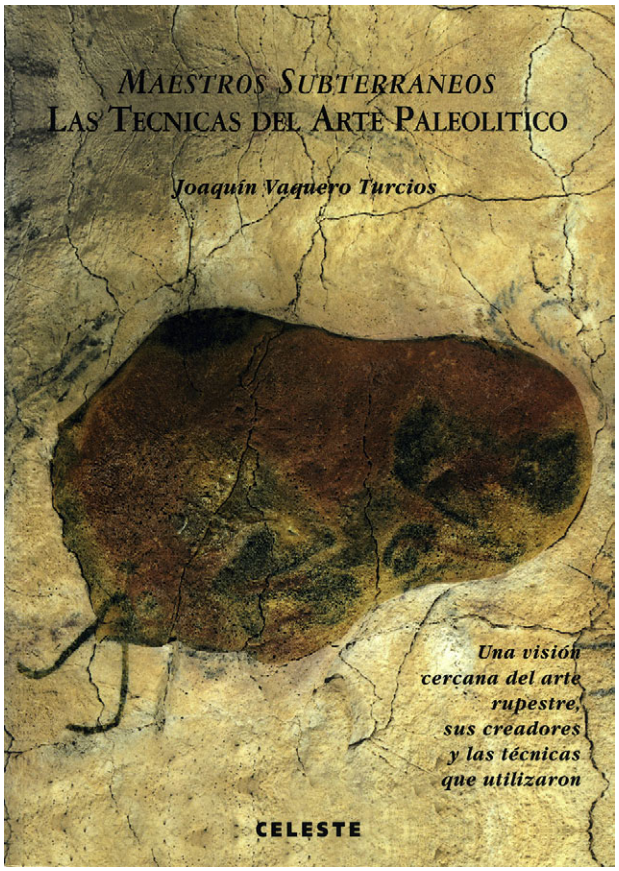

FIGURE 35.11 Cover of J. Vaquero Turcios' book (1995) about Paleolithic art, showing from Altamira a bison with the head turned. Translations: title, *Underground Masters: Techniques of Paleolithic Art*. Bottom right: "A close view of cave art, its creators and the techniques they used."

REFERENCES

Alexander, R., 1979. Darwinism and Human Affairs. University of Washington Press, Seattle.

Ayala, F.J., 1982. The evolutionary concept of progress. In: Almond, G.A., Chodorow, M., Pearce, R.H. (Eds.), Progress and Its Discontents. University of California Press, Berkeley, pp. 106–124.

Ayala, F.J., 1987. The biological roots of morality. Biology and Philosophy 2, 235–252.

Ayala, F.J., 2010. What the biological sciences can and cannot contribute to ethics. In: Ayala, F.J., Arp, R. (Eds.), Contemporary Debates in Philosophy of Biology. Wiley-Blackwell, Chichester, West Sussex, UK, pp. 316–336.

Ayala, F.J., Arp, R. (Eds.), 2010. Contemporary Debates in Philosophy of Biology. Wiley-Blackwell, Chichester, West Sussex, UK.

Bar-Yosef, O., Vandermeersch, B., 1993. El hombre moderno de Oriente medio. Investigación y Ciencia 201, 66–73.

Barash, D., 1977. Sociobiology and Behavior. Elsevier, New York.

Barkow, J., Cosmides, L., Tooby, J., 1992. The Adapted Mind: Evolutionary Psychology and the Generation of Culture. Oxford University Press, Oxford.

Bernardini, P.L., 2015. A note on the ethical value of aesthetics. Ndias Quarterly 3 (2), 19.

Blackmore, S., 1999. The Meme Machine. Oxford University Press, Oxford.

Bordes, F., 1953. Nodules de typologie paléolithique I. Outils musteriens à fracture volontaire. In: Bulletin de la Societé Préhistorique Française 50 Paris, vol. 1. Société préhistorique française.

Bordes, F., 1979. Typologie du Paléolithique ancien et moyen, vol. 1. CNRS, Paris.

Brosnan, S., de Waal, F., 2003. Monkeys reject unequal pay. Nature 425, 297–299.

Cela-Conde, C.J., Ayala, F.J., 2007. Human Evolution. Trails from the Past. Oxford University Press, Oxford.

Copp, D., 2006. The Oxford Handbook of Ethical Theory. Oxford University Press, Oxford.

Darwin, C., 1859. On the Origin of Species by Means of Natural Selection. John Murray, London.

Darwin, C., 1871. The Descent of Man, and Selection in Relation to Sex. John Murray, London (Also: Appleton and Company, New York, 1971).

Davidson, I., Noble, W., 1989. The archaeology of perception. Current Anthropology 30, 125–155.

de Waal, F., 1996. Good Natured: The Origins of Right and Wrong in Humans and Other Animals. Harvard University Press, Cambridge, MA.

DiMaggio, E.N., Campisano, C.J., Rowan, et al., 2015. Late Pliocene fossiliferous sedimentary record and the environmental context of early Homo from Afar, Ethiopia. Science 347 (6228), 1355–1359.

Doronichev, V., Golovanova, L., 2003. Bifacial tools in the lower and middle Paleolithic of the Caucasus and their contexts. In: Soressi, M., Dibble, H.L. (Eds.), Multiple Approaches to the Study of Bifacial Technologies. Museum of Archaelogy and Anthropology, pp. 77–107. Philadelphia, PA.

Gazzaniga, M.S., 2005. The Ethical Brain. Dana Press, New York.

Gazzaniga, M.S., 2008. Human. The Science Behind What Makes Us Unique. HarperCollins, New York.

Greene, J.D., Sommerville, R.B., Nystrom, L.E., Darley, J.M., Cohen, J.D., 2001. An fRMI investigation of emotional engagement in moral judgment. Science 293, 2105–2108.

Haidt, J., 2007. The new synthesis in moral psychology. Science 316, 998–1002.

Hamilton, W., 1964. The genetical evolution of social behavior. Journal of Theoretical Biology 7, 1–51.

Hauser, M., 2006. Moral Minds: How Nature Designed Our Universal Sense of Right and Wrong. Harper, New York.

Hume, D., 1740/1978. Treatise of Human Nature. Oxford University Press, Oxford.

Huxley, J., 1953. Evolution in Action. Harper, New York.

Huxley, T., Huxley, J., 1947. Touchstone for Ethics. Harper, New York.

Isaac, G.L., 1969. Studies of early cultures in East Africa. World Archaeology 1, 1–28.

Kitcher, P., 1985. Vaulting Ambition: Sociobiology and the Quest for Human Nature. MIT Press, Cambridge, MA.

Leakey, M.D., 1971. Olduvai Gorge 3. Excavations in Beds I and II 1960–1963. Cambridge University Press, Cambridge.

Leakey, M.D., 1975. Cultural patterns in the Olduvai sequence. In: Butzer, K.W., Isaac, G.L. (Eds.), After the Australopithecines. Mouton, The Hague, pp. 477–493.

Maienschein, J., Ruse, M., 1999. Biology and the Foundations of Ethics. Cambridge University Press, Cambridge.

Martineau, H., 1832–1834. Illustrations of Political Economy. in 9 vols, third ed. Charles Fox, London.

Moore, G., 1903. Principia Ethica. Cambridge University Press, Cambridge.

Noll, M.P., Petraglia, M.D., 2003. Acheulean bifaces and early human behavioral patterns in East Africa and south India. In: Soressi, M., Dibble, H.L. (Eds.), Multiple Approaches to the Study of Bifacial Technologies. University of Pennsylvania Museum of Archaeology and Anthropology, Philadelphia, pp. 31–53.

Paley, W., 1785. The Principles of Moral and Political Philosophy. Exshaw, Dublin.

Pinker, S., 2002. The Blank Slate: The Modern Denial of Human Nature. Viking, New York.

Plummer, T., 2004. Flaked stones and old bones: biological and cultural evolution at the dawn of technology. Yearbook of Physical Anthropology 47, 118–164.

Richerson, P.J., Boyd, R., 2005. Not by Genes Alone. How Culture Transformed Human Evolution. University of Chicago Press, Chicago and London.

Richerson, P.J., Boyd, R., Henrich, J., 2010. Gene-culture coevolution in the age of genomics. Proceedings of the National Academy of Sciences of the United States of America 107 (Suppl. 2), 8985–8992.

Ruse, M., 1995. Evolutionary Naturalism. Routledge, London.

Ruse, M., 2000. The Evolution Wars: A Guide to the Controversies. ABC-CLIO, Santa Barbara, CA.

Ruse, M., 2006. Darwinism and its Discontents. Cambridge University Press, Cambridge.

Ruse, M., 2010. The biological sciences can act as a ground for ethics. In: Ayala, F.J., Arp, R. (Eds.), Contemporary Debates in Philosophy of Biology. Wiley-Blackwell, Malden, MA, pp. 297–315.

Ruse, M., 2012. The Philosophy of Human Evolution. Cambridge University Press, Cambridge.

Ruse, M., Wilson, E.O., 1985. The evolution of ethics. New Scientist 108, 50–52.

Schick, K.D., Toth, N., 1993. Making Silent Stones Speak. Simon & Schuster, New York.

Sober, E., 1993. Philosophy of Biology. Westview Press, Boulder and San Francisco.

Sober, E., Wilson, D., 1998. Unto Others: The Evolution and Psychology of Unselfish Behavior. Harvard University Press, Cambridge.

Spencer, H., 1893. The Principles of Ethics. Williams and Norgate, London.

Strimling, P., Enquist, M., Eriksson, K., 2009. Repeated learning makes cultural evolution unique. Proceedings of the National Academy of Sciences of the United States of America 106, 13870–13874.

Vaquero Turcios, J., 1995. Maestros Subterráneos. Celeste Ediciones. S.A., Madrid.

Villmoare, B., Kimbel, W.H., Seyoum, C., et al., 2015. Early *Homo* at 2.8 Ma from Ledi-Geraru, afar, Ethiopia. Science 347 (6228), 1352–1355.

Waddington, C.H., 1960. The Ethical Animal. Allen and Unwin, London.

Webster's New Collegiate Dictionary, tenth ed., 1998. Merriam-Webster, Springfield, MA.

Whiten, A., Goodall, J., McGrew, W., et al., 1999. Cultures in chimpanzees. Nature 399, 682–685.

Whiten, A., Horner, V., de Waal, F., 2005. Conformity to cultural norms of tool use in chimpanzees. Nature 437, 737–740.

Wilson, E.O., 1975. Sociobiology, the New Synthesis. Belknap Press, Cambridge.

Wilson, E.O., 1978. On Human Nature. Harvard University Press, Cambridge, MA.

Wilson, E.O., 1998. Consilience: The Unity of Knowledge. Knopf, New York.

Wilson, E.O., 2012. The Social Conquest of Earth. Norton/Liveright, New York.

Wynn, T., 2002. Archaeology and cognitive evolution. Behavioral and Brain Sciences 25, 389–402.

Chapter 36

The Politics of Human Nature

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INTRODUCTION

> *The normal state for human beings is to be white, male heterosexuals. All others do not participate fully in human nature.*
>
> Hull, 1986, p. 7

> *L'espèce, c'est moi.*
>
> Sahlins, 2008, p. 2

An important political function of the vernacular concept of human nature is social inclusion/exclusion: it is involved in regulating who is "us" and who is "them," a process by which some people are *dehumanized*, ie, regarded as *not participating fully in what it means to be human*, as David Hull (1986) already stressed in his famous critique of the concept of human nature. This paper claims that dehumanization shows the concept of human nature to be a conceptual blank mold, a concept that is purely *functional*: it is filled—depending on context—with different content, but always with what *those speaking* consider to be *their* "essential" characteristics. Across context, the political dehumanization function remains constant, even if the content (what it means to be human) varies. It is in that sense that "l'espèce, c'est moi," as Marshall Sahlins (2008) wrote in his recent critique of the concept of human nature.

I distinguish between two ways of addressing the politics of human nature. There is, first, the politics of human nature that is *as a matter of fact regularly derived* from the concept of human nature. This refers to dehumanization and possible further political functions of the concept, such as an equality-establishing function (via the concept of *human* rights), a constraining function (ie, which life forms are possible for humans), or a responsibility-deferral function (via the idea that one is forced by human nature to do this or that). Dehumanization is the sole subject of this chapter. Second, there is the politics that can be philosophically *justified* with reference to human nature. I will not address this second issue at all, it being about whether political views can legitimately be based on knowledge about human nature. I rather assume that there is no justification in the name of human nature for *specific* political, economic, or social ideas, systems, etc. All we can derive from knowledge about humans are "some constraints on the possible development and behavior of the human organism," as John Dupré (2011, p. 162) stressed.[1]

In the following, I will show that the concept of human nature facilitates dehumanization independent of the content transported with "what it means to be human."

Section "Dehumanization" introduces dehumanization in a systematic manner. After providing some historical evidence in section "Evidence From History, Cultural Anthropology and Social Psychology," I will introduce a distinction between two forms of dehumanization in section "Two Forms of Dehumanization, From Explicit to Implicit" and add a short history of how dehumanization has been conceptualized in historical, ethnological, and psychological scholarship. The result, presented in section "Functional Perspective Necessary," is a *functional account* of the concept of human nature: the content of what it means to be human may well vary, but the function—that it facilitates dehumanization—endures.

DEHUMANIZATION

Dehumanization would not happen without a concept of human nature (ie, broadly understood: what it means to be

1. See also Reydon (2014) for a convincing, non-exhaustive taxonomy and critique of modes of "arguments from human nature" (as he calls them), arguments justifying specific political systems.

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00036-3

human) in the minds of those that dehumanize others.[2] Dehumanization can be defined as follows: an evaluative stance (merely cognitive or also behavioral) toward other humans that involves drawing a line between individuals or groups (as in-group/out-group) according to an assumed concept of what it means to be human.

Thus, even if all forms of dehumanization (that target a group of people) are cases of in-group favoritism (ie, out-group bias), not all forms of in-group favoritism are cases of dehumanization. Fast changing peer-group fashion codes might be an example of in-group favoritism without a connection to the concept of human nature. To count as a case of dehumanization, the process of inclusion/exclusion must have something to do with the concept of being human.

Dehumanization comprises three dimensions:[3]

1. It involves, first, holding a *seemingly factual* belief (eg, a projection or an overgeneralization, as in standard stereotyping) with respect to "being human," eg, a belief that "Jews are evil people and ruling the world," that "women are childlike and therefore not fully human," or that "Black men are aggressive rather than civilized and therefore not fully human."
2. It involves, second, an *emotive evaluation* leading to prejudice (eg, pity, disdain, superiority, fear, anger, or envy) as a cognitive stance.
3. Third, the cognitive-evaluative stance can have *behavioral consequences.* It can lead to diverse kinds of discrimination (ie, the social exclusion of ethnic groups, women, homeless people, etc.) and violence (eg, rape, war, genocide). Thus, socially important issues such as racism, sexism, eugenics, disability, poverty, as well as violence-related issues such as genocide and other forms of atrocity related to group conflicts are connected with dehumanization.

Dehumanization further commonly involves two contrasts, one between animals and humans and one between machines and humans. Humans are not like other animals, and they are not like machines. Consequently, there is *animalistic* dehumanization and *mechanistic* dehumanization, as Haslam (2006) calls these two basic forms of dehumanization that he suggests occur repeatedly and in various contexts. Smith (2011) sets a very narrow focus on cases of dehumanization that lead to aggressive behavior against those being dehumanized. He distinguishes dehumanization from:

- objectification (being regarded as object rather than subject);
- de-individualization (being regarded as an exemplar for a stereotype rather than an individual) (Smith, 2011, pp. 26–29).

Since objectifications can be regarded as a specific mechanistic form of dehumanization, and since de-individualization is a precondition for dehumanization, feeding into the first dimension, I rather opt for a broader focus and terminology. Dehumanization in the broad sense (as used here) includes a variety of forms of dehumanization. If one were to choose Smith's narrower meaning, then one would too easily overlook the systematic connections between objectification, de-individualization, and his narrow animalistic dehumanization. And it is these connections that social psychologists, studying dehumanization systematically, are interested in, when they use dehumanization in the rather broad sense used here.[4]

Dehumanization does not require essentialist thinking or even the use of the term "human nature," even though essentialist thinking and the language of human "nature" facilitates dehumanization.[5] What it does require is some vernacular concept of human nature, some understanding of what it descriptively means to be human.[6]

Given that dehumanization requires a concept of human nature, that concept thus plays a political role in interethnic conflicts and in a diversity of forms of dominance and oppression. What we think about human nature influences the way in which we treat other beings who we consider as being "not human" or "less human." We do not just employ the concept of human nature for "us"; we regularly use it to deny humanness to "them," eg, to out-groups or subgroups like women, behaviorally deviant people, strangers, pariahs, or enemies.

EVIDENCE FROM HISTORY, CULTURAL ANTHROPOLOGY, AND SOCIAL PSYCHOLOGY

Historians, cultural anthropologists and social psychologists have accumulated plenty of evidence of this darker,

2. That broad meaning of "human nature" can be further specified in a variety of ways. See Kronfeldner et al. (2014). Here, it will be primarily understood either as a descriptive concept, referring to a set of properties characteristic of the group of people called "humans," or as a classificatory concept, referring to properties (and be they relational) that make an individual human in the classificatory sense, ie, that decide about membership in the kind. These two meanings match two kinds of dehumanization: property- and heritage-related forms of dehumanization.
3. This ordering has been inspired by Mejias (2006).
4. See, for instance, Haslam (2006).
5. See Kronfeldner (2016), on why the language of human "nature" matters. A detailed argumentation for the claim that dehumanization happens even without essentialist thinking has to wait for another occassion.
6. See Footnote 2 for different ways of understanding the concept of human nature, including the anti-essentialist, minimal descriptive one of "what it means to be human" used here.

social side of the concept of human nature. In this section, I will present this evidence in an exemplary manner, with a focus on animalistic dehumanization. I will start with an example of dehumanization from the history of philosophy, namely the dehumanization of women as part of Aristotelian philosophy. I will then add a second contemporary example, the dehumanization of Africans and Amerindians.

Example 1.

Human nature in Aristotle can be understood as referring to the human life form, which is not only the *form* (contrasted with matter) but also the *end* (telos) of human flourishing. Within that frame, deviations are conceived as not fully realizing the form of the type (because of some interference). Aristotelian essentialism thus implied that variations in a species (eg, *Homo sapiens*) are deviations of a type. They are regarded as inferior to those more closely realizing the form, since *form is norm* within such an account. Women, for instance, were for Aristotle (infamously in *Politics*, Book 1, 1252a−1260b) such inferior deviations, deviations from human nature, and hence inferior to the free men representing the type.

To conceive of certain kinds of people being further away from a specific life form of a species involves making a distinction between proper and improper kinds of developmental causes. If a female is produced during reproduction, as Aristotle writes in the *Generatione Animalium* (GA $767^{b}7-25$), then "[n]ature has in a way departed from the type." He acknowledges that for sexually reproducing species it is a "natural necessity" that some females are produced. But he also holds that when they are produced, the embryo is "deficient," since if "the generative secretion in the catamenia is properly concocted, the movement imparted by the male will make the form of the embryo in the likeness of itself."[7] (The form of the embryo in Aristotle's picture is due to the male semen alone; women contribute matter only). Without any interfering causes, there would be no variation and only well-functioning Greek men, who had been conceived as realizing in full grandeur the nature of being human, or, in other words, representing the natural state of being human.

Aristotle still regarded women (despite their being deviants) as (what we now call) *Homo sapiens*, ie, as partaking in the same species as Greek men, as Deslauriers (1998) and Witt (2005) stress. It seems that variability within humankind did not prevent Aristotle from including the deviants as members of that one humankind, and consequently as partaking in the same human nature. The deviants were *same same, but different* (as an Asian idiom goes). (Subsequently, we will therefore distinguish between a form of dehumanization that concerns species membership and one that concerns exhibited properties.)

This explanatory schema in Aristotle's thinking involved teleological thinking. As Neil Roughley (2011, p. 13) describes it, "nature in this sense has dispositional to-be-realisedness, ie, in the absence of defeating conditions, the natural entity will realize its full and specific form." Consequently, the deviants (women in the example, but for Aristotle also the slaves and Barbarians of the ancient Greek world) were *less human*.

The explanatory schema was also essentialist in the sense that it picked out some features (such as rationality) as essential and contrasted them with other features that were deemed to be negligible for the essence of being human. In terms of the three dimensions of dehumanization, we can describe the case as follows: it is a case of (1) attributing more or less of *humanness* to a particular group in an overgeneralized manner that (2) very likely involved some emotional evaluation and (3) definitely had some behavioral consequences since men were supposed to be the masters of women and women had relatively limited rights in ancient Greek society.

In the 19th century, not much had changed, except the interpretation of the properties women were believed to lack, and the essentialist metaphysics beneath. Gustave Le Bon, for instance, founder-figure of social psychology, part of the craniologist movement and thus far from Aristotle's metaphysics, wrote: "In the most intelligent races, as among the Parisians, there are a large number of women whose brains are closer in size to those of gorillas than to the most developed male brains. This inferiority is so obvious that no one can contest it for a moment; only its degree is worth discussion. All psychologists who have studied the intelligence of women, as well as poets and novelists, recognize today that they represent the most inferior forms of human evolution and that they are closer to children and savages than to an adult, civilized man. They excel in fickleness, inconstancy, absence of thought and logic, and incapacity to reason. Without doubt there exist some distinguished women, very superior to the average man, but they are as exceptional as the birth of any monstrosity, as, for example, of a gorilla with two heads; consequently, we may neglect them entirely."[8]

I assume (and hope) that such a radical and explicit dehumanization is unlikely to arise in contemporary science. Yet, women are still regularly dehumanized, even if often only implicitly and not necessarily with respect to rationality or with respect to rationality alone.[9] The properties change, but the dehumanization endures. In addition, other humans are dehumanized with respect to still different

7. I am using the translation from Arthur Platt, which is part of the original Oxford edition (ed. by Ross, 1912).

8. Often quoted in feminist literature, after Gould (1978, p. 365).

9. For a general discussion of dehumanization and women, see Jaggar (1983), Nussbaum (1995), Haste (2000), and Mikkola (2011, 2016). For an empirical study, see Eyssel and Hegel (2012) and Koepke et al. (2014).

properties, eg, people of color with respect to aggression, as the next example illustrates. The *content*—the essential properties picked out—might well *change*, but the *function* of dehumanization *endures*.

Example 2.

Cases explicitly likening Africans and Amerindians (indigenous groups of North and South America) to great apes might be even more well-known by now than cases explicitly likening women to apes. The likening of Africans and Amerindians to apes is a form of dehumanization that is especially important in the context of colonialism and prevalent well into (if not way beyond) the 19th century, a time when abolitionists like the Darwin family were fighting racism. After Columbus's landfall in 1492, Spaniards hacked off natives' limbs, burned them alive and threw babies to the Spaniards' dogs. Some complained, eg, the Jesuit priest Montensinos, who asked "Are these not men? Have they not rational souls?" Even in the 16th century, humanist scholars such as Giordano Bruno and the alchemist Paracelsus, among others, denied a shared ancestry of *their* people with *those* Amerindians, regarding them as *non-Adamic* in origin (as *not* descending from Adam, the common denominator of the Judeo-Christian-Islamic androcentrism), or by regarding them as *homunculi*: beings with a human body but no soul.[10] In the 19th century, when Charles Darwin was traveling on the *Beagle*, it was still common in certain areas of the world to regard in particular Afro-American people as a *separate* species, an intermediate step between brutes and humans, as Desmond and Moore (2009) report in their new biography on Darwin. Darwin, as a member of a family fighting for the abolition of slavery, also had a "sacred cause" to write his *Origin of Species*: to develop a theory of evolution that relied on *common* descent in order to show that the racism underpinning slavery was scientifically wrong.

Implicitly, the association between "Black" people and apes is still active today, as Goff et al. (2008) demonstrate in a set of experiments. Their first experiment, a degraded object test, already showed an implicit bias that they name the "Black-ape facilitation effect." Study participants are first subliminally primed with black, white, and neutral faces. They then have to recognize degraded line drawings of animals that gradually become easier to identify. The prediction is (for White as well as non-White study participants): "exposure to the Black male faces would facilitate identification of the ape images, whereas exposure to the White male faces would not." Debriefing confirmed that participants were not aware of priming faces. Completion of the Modern Racism Scale and the Motivation to Control Prejudice Scale were used to make sure that the results were independent of individual differences in explicit anti-Black prejudice or attitudes about prejudice. The results are illustrated in Fig. 36.1.

When primed with Black faces (black columns), fewer frames are needed to identify the ape images compared to non-ape images, and compared to when study participants are not primed (grey columns). When primed with White faces (white columns), more frames are needed to recognize the ape images compared to the non-ape images, and compared to when study participants are not primed (grey column). Images of Black faces facilitate ape recognition. Further experiments added the following points: first, the effect is bidirectional (images of apes also facilitate attention to Black faces) and, second, the effect is specific for Black people (rather than a general out-group bias, since analogous tests with Asian faces did not show the same results). By using colorless line drawings, they tried to rule out the possibility that the effect was due to simple perceptual color matching. By also testing associations with other animals (eg, big cats such as lions that are also stereotypically perceived as being aggressive), they tried to rule out that what they were observing was simply an association with aggression, rather than a specific Black-ape association. Yet, aggression seems to play a role in the specific Black-ape association.

In two further studies, Goff et al. sought to establish whether also judgment (rather than only perception and

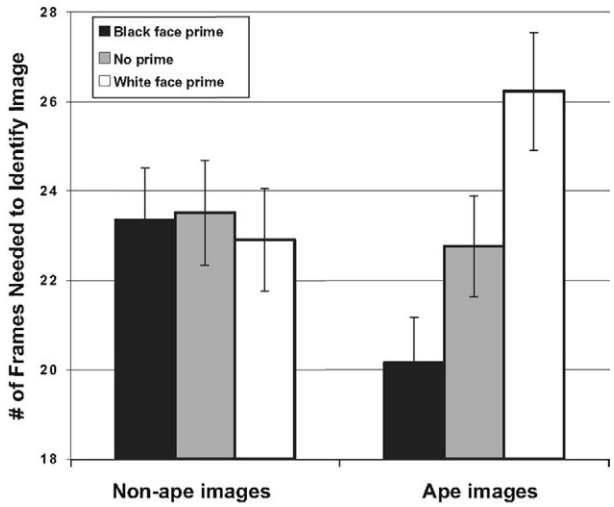

FIGURE 36.1 Results of the degraded object test study. The original caption says: "Mean frame number at which the animal could be detected as a function of animal type and race prime (Study 1). Error bars represent the average standard error for each condition." *From Goff, P.A., Eberhardt, J.L., Williams, M.J., Jackson, M.C., 2008. Not yet human: implicit knowledge, historical dehumanization, and contemporary consequences. Journal of Personality and Social Psychology 94, 296.*

10. The quotation from Montesinos and further references regarding that history can be found in Smith (2011, p. 77ff), also with respect to the famous month-long debate between Sepúlveda, an Aristotelian scholar defending the notion that indigenous people are natural slaves, and Bartolomé de Las Casas, defending their status as equally human. For a in-depth study of likening people to apes, see Hund et al. (2016).

cognition) is influenced by the Black-ape association. First, they studied whether priming with ape images and big cat images influences the judgment whether police violence against suspects (shown to study participants in a video) is justified. The results (among other things) showed that violence against Black people was more likely to be regarded as justified, when participants were primed with ape images. Their final, historical (rather than experimental) study on death sentences in Philadelphia between 1979 and 1999 adds evidence in the same vein. Goff et al. (2008, p. 304) conclude with respect to the latter: "Black defendants are more likely to be portrayed as apelike in news coverage than White defendants and that this portrayal is associated with a higher probability of state-sponsored executions."

TWO FORMS OF DEHUMANIZATION, FROM EXPLICIT TO IMPLICIT

I take it that in the 21st century it is unlikely that somebody *explicitly* regards other people as (1) members of a *different species* or as (2) *like* apes. Thus, explicitly denying (1) membership in humankind and (2) humanness should be rather rare. An exception, at least for (2), is propaganda and caricature, as in the following famous poster that combined the dehumanization of women and enemies simultaneously (Fig. 36.2).

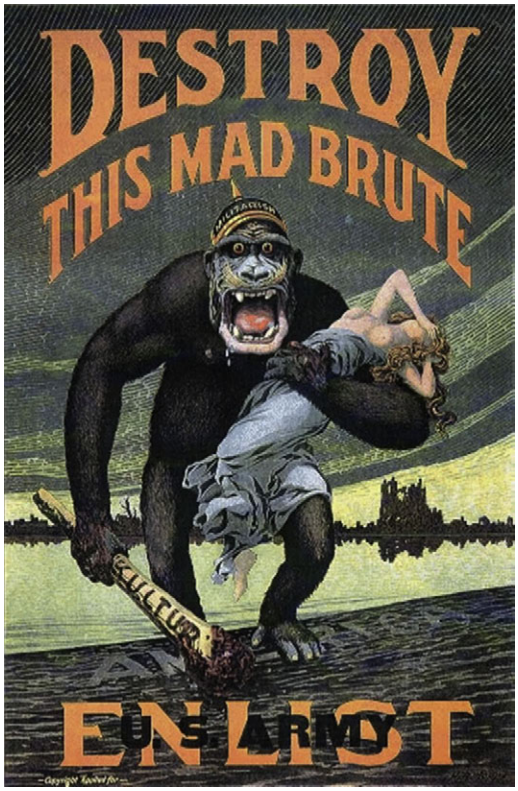

FIGURE 36.2 Army poster encouraging US soldiers to enlist in the army. The enemy was WW1 Germany. Ca. 1917 (public domain, picture at Harry Ranson Center, University of Texas, Austin).

In addition to a very likely ongoing explicit dehumanization in propaganda and caricature, people might still implicitly be regarded in all kinds of contexts as less human in the two forms just mentioned, ie, as less human: (1) in heritage (*heritage-related dehumanization*) or (2) with respect to humanness, ie, with respect to properties such as rationality or civility versus aggression or any other putative "essential" property of being human (*property-based dehumanization*). In such an implicit form, (1) membership in humankind or (2) instantiation of "essential" properties is not denied, but graded.

Given these two forms of animalistic dehumanization, the results, especially of the last two studies by Goff et al. (2008) can be explained either by (1) a heritage-based exclusion attitude of *Black-means-apelike-means-less-human-by-heritage-and-therefore-not-as-much-protected-by-human-rights* or by (2) a specific triadic association of *Black-means-apelike-means-aggressive-and-therefore-exhibiting-less-humanness*. I concede the difficulty of deciding which form of dehumanization is taking place, but the important issue is that they both can happen and can be distinguished from each other.

I thus conclude that implicit dehumanization in both these forms is still among us and likely to be very widespread. I take the evidence accumulated in social psychology, reviewed in Haslam and Loughnan (2014), to confirm this.

FUNCTIONAL PERSPECTIVE NECESSARY

Before I add theoretical background from historical, ethnological, or psychological scholarship, let me draw *a first philosophical conclusion*: the *content* of the concept of human nature (eg, that rationality is part of human nature, or that other animals are aggressive and humans civilized) changes historically and varies between people and scientific contexts. The aforementioned examples illustrate the following:

- a change from Aristotelian metaphysics to the craniologist movement with respect to the dehumanization of women;
- a change from colonial dehumanization of Amerindians as non-Adamic in heritage or as homunculi, to the Black-ape facilitation effect;
- ways in which different traits can be used to liken people to apes. (Recall the list from Le Bon for women and compare it with the role of aggressiveness in the Black-ape facilitation effect.)

Despite changes in content, the concept of human nature has not changed its *function*, namely *social inclusion/exclusion*, ie, including *this* kind of people and excluding

that kind of people, regulating who is "us" and who is "them." That means the function of the concept endures, even if the content may well vary.

A philosophy of science point of view on the concept of human nature should thus not restrict itself to the *content* of the concept of human nature as such (since it changes throughout history anyway). It should acknowledge the *function* the concept plays in the social realm. After all, the function is much more stable across contexts.

I take the results of other experimental studies on dehumanization in social psychology to converge on such a functional perspective, despite differences in details, as described in overview by Haslam and Loughnan (2014).[11] I also take the history of theorizing about dehumanization to also confirm that functional perspective. David Hume (in his *Treatise*, as part of his analysis of love and hate, Book II, Part 2, Sect. 3) has already discussed sympathy as a bias that favors members of one's own group and dehumanizes others. The anthropologist and sociologist Graham Sumner (1906, pp. 12–15) then established "ethnocentrism" as a technical term for a dehumanizing out-group bias and stressed how widespread it is, since "[a]s a rule, it is found that nature peoples call themselves 'men.' Others are something else—perhaps not defined—but not real men" (Sumner, 1906, p. 14). Examples Sumner mentioned for the (1) heritage-related form of dehumanization were Caribbeans, Kiowa, Lapps, Greenland Eskimos, and Tunguses. Others, he writes, exhibit a less strong dehumanizing ethnocentrism, by believing in various kinds of superiority, ie, that others are less human in sense (2) specified earlier. Sumner mentions Ainos, Jews, the Chinese, Greeks, Romans and Arabs of antiquity. Lévi-Strauss (1952, p. 12) then, famously, put the mindset of ethnocentrism as follows: "Humanity is confined to the borders of the tribe, the linguistic group, or even, in some instances, to the village." He also stressed a specific reciprocity, namely the reciprocity of dehumanization attitudes: "In the Greater Antilles, some years after the discovery of America, while the Spaniards sent out investigating commissions to ascertain whether or not the natives had a soul, the latter were engaged in the drowning of white prisoners to verify, through prolonged watching, whether or not their corpses were subject to putrefaction."

The Spaniards were skeptical about the humanness of the natives in terms of them "having a soul," whereas the natives were skeptical about the humanness of the Spaniards in terms of them "having life" (tested by whether the decaying pattern characteristic for life occurs). The first was a case of animalistic dehumanization, the second a case of mechanistic dehumanization.

I conclude from all this anthropological and psychological research: the specific *form* of dehumanization varies with the *content*, but—again—the *function* of excluding those regarded as others from being human in the full sense remains the same. Only such a functional perspective can explain the *reciprocity* of dehumanization that Lévi-Strauss stressed.

Lévi-Strauss fought ethnocentrism as the psychological underpinning of racism, which he regarded as being (in part) responsible for the Holocaust and other war-related atrocities during WWII. Dehumanization is clearly involved in some but not necessarily all group-related violence.[12] But as mentioned earlier, dehumanization as understood here does not have to be connected with violence. It is a much more unbound phenomenon, much more widespread and often quite implicit, as Goff et al.'s (2008) studies show. Dehumanization not only manifests itself in group conflicts or other kinds of violent or oppressive behavior. It is, as I have stressed, everywhere and has consequently to be systematized from a functional perspective: the details vary (general forms as well as specific properties that are regarded as essential for humanness), but the function of inclusion/exclusion endures.

The historian Reinhart Koselleck (2006 [1993], p. 279) concluded from historical material that actually the concept of "being human" is historically viewed a "blank mold" ("Blindformel") only. In contrast to other historical asymmetric concepts for collectives, such as "Christian" leading to concepts for enemies ("Feindbegriffe" eg, the non-Christians), "human" is a conceptual blank mold ("Blindformel"). It is a conceptual blank mold since *any group can fill it with what that group is like* and exclude the respective others as being *less human*. *L'espèce, c'est moi* (to use Sahlins' ingenious words again), all others are less human. I take Smith (2013) to agree on this, when he claims that "being human" is a term that is indexically used, like "being here."[13]

CONCLUSION AND OUTLOOK

To conclude: dehumanization is *ubiquitous*, *reciprocal*, and there is a central *exchangeability* of the content of what it means to be human. The vernacular concept of being human/human nature has to be understood from a functionalist perspective, since there is an independence between the dehumanization function of these concepts and

11. As a side note: this functional perspective also helps to understand why the concept of human nature has such a great (and even normative) authority in science. For that topic, see Kronfeldner (2016).

12. For book-length historical and further anecdotal evidence, consult Smith (2011).

13. An indexical term like "being here" is contrasted with substantive terms like "water" that stand for specific substances.

the varying contents that might be filled into the terms "being human"/"human nature." These terms are like indexicals.

Yet one might ask: doesn't science give us some *objective content* for the concept of being human/human nature? It does, since any approach from contemporary science that uses the concept of human nature will try to remove the indexicality in the vernacular concept. Yet, these approaches will have their own problems that lead to an open-ended list of scientific disagreements, as described in Kronfeldner (2016). In addition, filling the concept of human nature with objective content will not resolve the politics of human nature. As long as the sciences say something on heritage or humanness, it holds that these sciences can be used for each respective form of dehumanization, ie, heritage-based or property-based dehumanization. Illustrating this in detail and elaborating on what follows from this for these sciences needs to be the subject of future research. The basic point that I want to make here can be summarized as follows.

Even given that it is regarded as a scientific fact that all currently living humans belong to the same one species, some can be regarded as being less human. Genealogy allows for grading within the one humankind since a genealogical relationship can be more or less direct. The Black-ape facilitation effect can thus be explained by (and would be predicted) on the sole basis of a belief in a *different or at least more distant heritage* of a Black person to a White person (compared to the genealogical distance between a White person to another White person). Such a belief in an individual's genealogical distance does not need to rely on phenotypic properties such as skin color, it can go deeper as in current use of genetic modeling of ancestry.[14] Furthermore, it might (but does not have to) involve a belief in races, separate groups united only indirectly far back in history by a common human ancestor. Dehumanization can thus utilize racism in the sense of a belief in human groups that are genealogically (ie, reproductively) isolated to a certain degree so that they can now be regarded as real taxonomic units, as separate groups. If such genealogical racism combines with a dehumanizing ethnocentrism, *same close heritage* is all that would count in such a mindset as a criterion for being fully human or not. The closer genealogically related, the more human - that would be the "logic" of that contemporary variant of heritage-based dehumanization. It is a matter of historical and sociological study, whether such a form of dehumanization is still widespread, but I assume that it can exist and that it is likely to be the basis of some forms of contemporary racism, given that genealogy has been used historically for the dehumanization of ethnic groups with a specific geographic origin (eg, in the case of the Amerindians or Afro-Americans as non-Adamic in heritage). As long as genealogy is used for delineating biological kinds, it can be used to regard some individuals as *not* human or as *less* human. As long as that delineation is politically relevant (which does not have to be the case but might often be the case), this dehumanization is politically relevant too.[15]

If the term human nature means nothing but a set of properties that are widespread within humankind, then these properties can still be differentially applied to outsiders. Human nature would thus simply refer to contingent generalizations about humans (eg, that "we" use spoken language, walk upright, have opposable thumbs). These generalizations still have dehumanizing potential since those individuals that do not conform to the generalizations can still be dehumanized. Any case of ableism or contemporary eugenics would be a case in point of such non-essentialist dehumanization.[16] As long as the majority rules (descriptively and socially) in science and society, those not in the majority can face some discrimination in terms of being regarded as less human. Thus, dehumanization can take place on the basis of an objective concept of human nature too. Furthermore, which generalizations are regarded as *important* for the respective life form might well vary across cultures. Since there will always be a plentitude of properties that are widely shared among humans, talk about human nature (even in sciences) will involve a choice of those properties. As mentioned elsewhere (Kronfeldner, 2016), an interesting under-determination results: certain properties can be prioritized without science giving you any foundation in objective facts for the priority chosen. Some researchers will highlight rationality, others morality, still others the opposable thumb, or some other trait. As in all cases of under-determination, not only disciplinary focus but also social values will govern the choice of what is most important for "being human," with often no scientific way of finding agreement on the result.

Given that both forms of dehumanization can persist even given an objective concept of human nature, how can sciences limit the danger of dehumanization? Given the

14. See Olson (2002) on this issue.

15. Where exactly to draw the line (given that genealogy is a transitive relation) is certainly always a pragmatic and equally politically important decision, as Hull (1986), Antony (2000), and Proctor (2003) stressed. For instance, in paleoanthropology, given the lack of evidence, there is a thorough even though contingent under-determination of theory by data. Consequently, one can choose to dehumanize the Neanderthals. One can be more strict (ie, more exclusive) or choose to include them by being less strict (ie, more inclusive) in drawing the line of where "our" species began. Given that under-determination, Proctor (2003) has argued, how ex/inclusive a society is has an effect on how ex/inclusive the respective "science" is, highlighting thus an interesting mingling of science and society.

16. See St. Pierre and Wilson (2016) on eugenics and Wolbring (2008) on ableism.

authority in the term "nature" (as described in Kronfeldner, 2016), eliminating the language of "human nature" (to rather speak of widespread properties or a specific heritage) is a suggestion that has been in existence since Hull's (1986) famous critique of the concept. Eliminating the language of human nature might help to keep dehumanization in check, but its elimination might also have negative consequences. Only a detailed analysis of how to balance the risks of misuse and the social and scientific prize of elimination can provide a convincing answer to this question.

ACKNOWLEDGMENTS

I want to thank Alexander Reutlinger for his inspiring critical thoughts on this paper and Friederike Eyssel as well as Edouard Machery for their helpful hints and references. Some of the ideas that ultimately found their way into this paper have been presented as visiting fellow of the research group on "Twentieth Century Histories of Knowledge About Human Variation," (directed by Veronika Lipphardt, *Max Planck Institute for History of Science* (MPIWG) in Berlin), at the 2014 meeting of the *Deutsche Gesellschaft für Geschichte und Theorie der Biologie e.V.*, at the *2. Workshop of the Society for Women in Philosophy Germany e.V.*, at the 2015 meeting of the *International Society for History, Philosophy and Social Studies of Biology* (ISHPSSB), and at the 2015 human nature course at the *Central European University* (CEU), Budapest. Many thanks to the audiences present and to the organizers, especially to Rob Wilson, who co-organized with me the ISHPSSB session, and to my students, who were such amazing critics. Special thanks to Veronika Lipphardt and her group for the kind hospitality at the MPIWG.

REFERENCES

Antony, L.M., 2000. Natures and norms. Ethics 111, 8–36.

Aristotle, 1912. The Works of Aristotle, vol. 5. In: Ross, W.D. (Ed.), Oxford University Press, Oxford.

Deslauriers, M., 1998. Sex and essence in Aristotle's metaphysics and biology. In: Freeland, C.A. (Ed.), Feminist Interpretations of Aristotle. Pennsylvania State University Press, University Park, PA.

Desmond, A.J., Moore, J.R., 2009. Darwin's Sacred Cause: Race, Slavery and the Quest for Human Origins. Penguin, London.

Dupré, J., 2011. What is natural about human nature? In: Gethmann, C.F. (Ed.), Lebenswelt und Wissenschaft. XXI. Deutscher Kongreß für Philosophie. Kolloquiumsbeiträge. Meiner, Hamburg, pp. 160–171.

Eyssel, F., Hegel, F., 2012. (S)he's got the look: gender stereotyping of robots. Journal of Applied Social Psychology 42, 2213–2230.

Goff, P.A., Eberhardt, J.L., Williams, M.J., Jackson, M.C., 2008. Not yet human: implicit knowledge, historical dehumanization, and contemporary consequences. Journal of Personality and Social Psychology 94, 292–306.

Gould, S.J., 1978. Women's brains. New Scientist 364–366.

Haslam, N., Loughnan, S., 2014. Dehumanization and infrahumanization. Annual Review of Psychology 65, 399–423.

Haslam, N., 2006. Dehumanization: an integrative review. Personality and Social Psychology Review 10, 252–264.

Haste, H., 2000. Are women human? In: Roughley, N. (Ed.), Being Human. de Gruyter, Berlin, pp. 175–196.

Hull, D.L., 1986. On human nature. PSA: Proceedings of the Biennial Meeting of the Philosophy of Science 2, 3–13.

Hund, W.D., Mills, C.W., Sebastiani, S., 2016. Simianization: Apes, Gender, Class, and Race. LIT, Zürich.

Jaggar, A.M., 1983. Feminist Politics and Human Nature. Rowman & Allanheld, Totowa, NJ.

Koepke, S., Eyssel, F., Bohner, G., 2014. "She deserved it": effects of sexism norms, type of violence, and victim's pre-assault behavior on blame attributions toward female victims and approval of the aggressor's behavior. Violence Against Women 20, 446–464.

Koselleck, R., 2006. Feindbegriffe. In: Begriffsgeschichten: Studien zur Semantik und Pragmatik der politischen und sozialen Sprache. Suhrkamp, Frankfurt/Main, pp. 247–284.

Kronfeldner, M., Roughley, N., Toepfer, G., 2014. Recent work on human nature: beyond traditional essences. Philosophy Compass 9, 642–652.

Kronfeldner, M., 2016. Divide and conquer: the authority of nature and why we disagree about human nature. In: Lewens, T., Hannon, B. (Eds.), Why We Disagree About Human Nature. Oxford University Press, Oxford (forthcoming).

Lévi-Strauss, C., 1952. Race and History. UNESCO, Paris.

Mejias, M., 2006. Staircase of Dehumanization [WWW Document]. URL. http://resources.mhs.vic.edu.au/mockingbird/downloads/StaircaseofDehumanization.pdf.

Mikkola, M., 2011. Dehumanization. In: Brooks, T. (Ed.), New Waves in Ethics. Palgrave-MacMillan.

Mikkola, M., 2016. The Wrong of Injustice: Dehumanisation and Its Role in Feminist Philosophy. Oxford University Press, New York.

Nussbaum, M.C., 1995. Aristotle on human nature and the foundations of ethics. In: Altham, J.E.J., Harrison, R. (Eds.), World, Mind and Ethics: Essays on the Ethical Philosophy of Bernard Williams. Cambridge University Press, Cambridge, pp. 61–104.

Olson, S., 2002. Mapping Human History: Discovering the Past Through Our Genes. Houghton Mifflin, Boston.

Proctor, R.N., 2003. Three roots of human recency: molecular anthropology, the refigured Acheulean, and the UNESCO response to Auschwitz. Current Anthropology 44, 213–239.

Reydon, T.A.C., 2014. The evolution of human nature and its implications for politics: a critique. Journal of Bioeconomics 17, 17–36.

Roughley, N., 2011. Human natures. In: Schleidgen, S., Jungert, M., Bauer, R., Sandow, V. (Eds.), Human Nature and Self Design. Mentis, Paderborn, pp. 11–33.

Sahlins, M., 2008. The Western Illusion of Human Nature. Prickly Paradigm Press, Chicago.

Smith, D.L., 2011. Less Than Human: Why We Demean, Enslave, and Exterminate Others. St. Martin's Press, New York.

Smith, D.L., 2013. Indexically yours: why being human is more like being here than it is like being water. In: Lanjouw, R.C.A. (Ed.), The Politics of Species: Reshaping Our Relationships With Other Animals. Cambridge University Press, pp. 40–52.

St. Pierre, J., Wilson, R., 2016. Eugenics and disability. In: Devlieger, P., Rusch, F., Brown, S., Strickfaden, M. (Eds.), Rethinking Disability. Garant Publishing.

Sumner, W.G., 1906. Folkways: A Study of the Sociological Importance of Usage, Manners, Customs, Mores and Morals. Ginn, Boston.

Witt, C., 2005. Form, normativity and gender in aristotle: a feminist perspective. In: Alanen, L., Witt, C. (Eds.), Feminist Reflections on the History of Philosophy. Springer, Netherlands, pp. 117–136.

Wolbring, G., 2008. The politics of ableism. Development 51, 252–258.

Chapter 37

The Race/Ethnic Debate: An Outsider's View

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LIST OF ABBREVIATIONS

AIM Ancestry informative marker
CV Common variant
HGDP Human genome diversity project
HLA Human leukocyte antigen
LFV Low frequency variant
RV Rare variant
SNP Single nucleotide polymorphism
WGS Whole genome sequencing

***La Nature se rit de nos classifications*. "Nature, although inexhaustible in her combinations, nevertheless does not proceed through jumps and jerks; on the contrary, it is through imperceptibly processed transitions that she incessantly spins the immense chain of organized beings; it is through links of an imperceptible texture that she binds together all what spreads, vegetates or breathes. We design classifications and methods with great pain and art, and she laughs at our methods and classifications." (French Société Polytechnique, 1827)**

Being neither a social or biological anthropologist, nor a human geneticist, I can be considered a naïve outsider in this debate. However, as an MD and the editor-in-chief of a scientific journal reporting on human genetic susceptibility to transmissible diseases (among other topics), I have closely followed the debate on the medical relevance of races, ethnic groups, geographical populations, and so forth. PhD-trained in population genetics and zoology (parasitology, medical entomology), I have taken a keen interest in exploring the taxonomical problem of human genetic diversity within a broad framework based on comparisons with other living organisms. My view, which I assume is shared by all biologists, is that human beings should be studied with the same genetic and evolutionary concepts as other living creatures. Building specific population genetics for humans, isolated from that of other living creatures, could be grossly misleading. Science demands comparisons in order to establish general laws that aim at being as broad as possible. Now, due to tragic historical events (colonization, eugenics, Nazism), it is obvious that the debate on human races cannot be as smooth as exploring the taxonomy of newts or carabid beetles. The term "race" (or the adjective "racial") continues to be used by many scientists, both in social (Eberhardt, 2005; Kubota et al., 2012) and biological sciences (Belizário, 2013; Need et al., 2009; Risch et al., 2002; Tang et al., 2005). However, there is no doubt that the term is ideologically loaded. The very use of this term is therefore debatable (see later in this chapter). Morals, ethics, and politics have much to say in this matter. However, morals, ethics, and politics should not interfere with science, and vice-versa. I will try to present below both the biological and social sides of the debate. The biological discussion will be limited to the taxonomical and evolutionary questions underlying the concept of race. Never-ending debates on compared cognition, IQ, and sports performance will not be developed in this chapter. Lastly, since the field is controversial, exact, complete citations will often be used to avoid misunderstandings.

WHERE ARE WE NOW: HUMAN GENETIC DIVERSITY IN LIGHT OF MODERN GENOMICS

Chapter 6 specified the main advances of modern genomics in human population diversity. Chapter 10 detailed the medical relevance of this diversity. Only a brief review will be given here.

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00037-5

Modern genomics uses powerful tools that have fallen in cost considerably in recent years. The sequencing of a human genome, which required several years in past heroic times, now requires only a few days, even a few hours (Kollewe, 2012), and a few 1000 USD. This makes it possible to sequence the genomes of not only individuals, but also populations. However, whole-genome sequencing (WGS) of entire populations remains costly. Populations can be characterized at lower costs with multiple markers, called single nucleotide polymorphisms (SNPs). Today studies using 500,000 to 1 million SNPs are not exceptional. WGS and modern markers have made it possible to confirm and considerably refine the results gathered by pioneering studies from as early as the 1970s (Lewontin, 1972; Nei, 1978). The main results are as follows:

1. With common genetic markers, most of the genetic variation is uncovered among individuals of the same continental group (for example, Europeans). Genetic variation among continental groups ranges from 5% to 15% depending on the sample and the markers used.
2. When the genetic differences among populations are used to compute evolutionary trees, the major continental groups are clearly evidenced (see Figs. 6.1–6.4 in Chapter 6) whatever population sample and markers are used, with few differences from one study to another. The apparent contradiction between proposals (1) and (2) comes from the fact that the statistics used in (1) (see "The *F*st Argument") consider each genetic locus in isolation, while the 5–15% of the loci that show differences among continental groups are correlated, that is to say, they give convergent results (Edwards, 2003).
3. The major continental groups uncovered by genetic markers do not show strict separations and exhibit some overlapping, often with intermediary populations (such as Ethiopians).
4. Genetic variation is not strictly clinal. If human populations were clinal, they would vary continuously and would be strictly correlated with geographical distance. Major geographical obstacles (oceans, the Himalayas, the Sahara) have impacted the clustering pattern revealed by genetic markers.
5. When modern markers are used, it is possible to reliably assign not only populations, but also individuals to their geographical origin. Ancestry informative markers (AIMs) are even able to reliably evaluate the degree of admixture of any individual and are widely used in forensic medicine and biomedical research.
6. While most common variants (CVs; frequency $\geq$5%) are found in all major continental groups, most variants actually correspond to low-frequency variants (LFVs; frequency, 0.5–5%) and rare variants (RVs; frequency, $\leq$0.5%). LFVs and RVs play a much more important role in determining phenotypes and diseases than CVs. They tend to be geographically localized, originated recently, and are related to recent, local adaptations. The rarer they are, the more localized and recent they tend to be.
7. The massive use of a great number of genetic markers reveals that major continental groups are far from being homogeneous and exhibit considerable population stratification (Russian doll structure; Tibayrenc and Ayala, 2013). The analysis of these lesser populations may have great medical relevance (see Chapter 10).
8. Modern genomics has shown that most present populations in the world are the result of complex past admixtures.
9. Genes involved in disease (both Mendelian diseases and common diseases; see Chapter 10), as well as disease-resistance variants, often have an uneven distribution among ancestry groups.
10. Lastly, many recent studies have provided convergent evidence for geographically localized, abundant, recent adaptation. Much natural selection is assumed to have acted after the out-of-Africa (OOA) migrations on populations undergoing different climatic and diet conditions, submitted to diversified pathogen pressures. Natural selection may not have stopped with the emergence of modern humans 40,000–50,000 years ago, as was classically thought, but instead may have strongly impacted human populations until recently, and probably still does. The proposal of recent, localized evolution has been pushed by two recent popularization books (Cochran and Harpending, 2009; Wade, 2015). Since these books presented controversial hypotheses about cognitive evolution, they have been fiercely debated (de Praconval, 2009; http://shrinkwrapped.blogs.com/blog/2009/01/a-most-dangerous-book.html; Gelman, 2014; Graves, 2014; Marks, 2014). However, the hypothesis of recent, local adaptation has been supported by many scientific publications (see Chapter 6).

To complement this summary on the results coming out of modern genomics, it should be remembered that morphometric data, in particular dental and craniometric measures, parallel those of genetics (see Chapter 6). There is strong variability within major continental groups with overlapping among them. However, morphometry makes it possible to accurately identify the geographical origin of individuals (Edgar, 2009; Ousley et al., 2009; Relethfod, 2009). The classic view that cranial morphology was poorly heritable and strongly influenced by the

environment (Boas, 1912) has been challenged (Sparks and Jantz, 2002).

THE TAXONOMICAL PROBLEM: ARE THERE "RACES"?

Semantic Clarification Is Needed

To answer this question, considerable semantic clarification is needed to define what is understood by the term "race." Science begins with clear definitions, and bad science enjoys building its definitions on sand. Unfortunately, as noted at the beginning of this chapter, "Nature laughs at our classifications." An Editorial in Nature Genetics in 2000 noted that the terms "race" and "ethnic group" had a diversity of definitions. This is also the vision defended by Edgar (2009). However, the same remark could also be made for the definition of "species." Hey (2001) counted no fewer than 24 different species concepts. I have highlighted (Tibayrenc, 2006) the best species concept I know: "a species is what a wise and competent specialist thinks to be a species." This could possibly be applied to the definition of race. Actually, when one tries to apply very strict definitions to any taxonomical concept, it escapes as fast as sand slips through your fingers. What are the strict evolutionary definitions of classes, orders, families, and genera? There are none. They are defined only by their rank.

Let Us Speak of Biology Only

To come back to human races, as a start I will limit the discussion to the biological definition of race. In lay vocabulary, the concept of race may include cultural aspects that have nothing to do with biology. Sometimes race, ethnicity, culture, and citizenship are confused (Betancourt and López, 1993). Vallois (1976) called for caution when approaching this semantic confusion and recommended anchoring the race concept in anthropology on biological grounds only. Interestingly, it is with the goal of separating these cultural aspects from the biological aspect that Georges Vacher de Lapouge, considered one of the fathers of racist thought in Europe (although a socialist), coined the term of *ethnie* (ethnic group). According to this original meaning, an ethnic group is composed of people of different races (based on the biological meaning) sharing the same culture. Mersha and Abebe (2015) noted than Germans and French pertain to the same Caucasian *race*, but have a different *ethnicity*.

Race Detractors Versus Race Realists

When race is restricted to the biological viewpoint, two opposite positions are encountered: (1) race detractors, who believe race is a pure social concept and has no biological reality and (2) race realists (Malik, 2012), who believe race has some biological reality, is not only a mere vision of the mind, and could be a usual proxy for biomedical studies. These are the two polar concepts discussed in the scientific community. We will not consider the extremist thought that claims that race differences, chiefly including cognitive ability, are 100% explained by biology and hence that races should be (are obviously) hierarchized (ethnomaniacs; Hooton, 1926). To my knowledge, this view is not defended by any scientist. The supporters of racial IQ differences themselves (Arvey et al., 1994; Herrnstein and Murray, 1994; Rushton and Jensen, 2006) recognize that environment and education play an important role in IQ racial differences.

Concept (1) is defended by many social scientists and currently increasing numbers of biologists. The view that races have no biological reality has been officially claimed by the American Association of Anthropologists' statement on race (1998), which asserts that many anthropologists considered that race was a social concept forged in the 18th century to justify slavery: "It has become clear that human populations are not unambiguous, clearly demarcated, biologically distinct groups… Throughout history whenever different groups have come into contact, they have interbred. The continued sharing of genetic materials has maintained humankind as a single species… Any attempt to establish lines of division among biological populations is both arbitrary and subjective." This statement did not reflect a consensus of all members of the AAA. However, it was considered "that it represents generally the contemporary thinking and scholarly positions of a majority of anthropologists." The view that race has no biological basis, or at least no satisfactory biological definition and is mainly a social construct, was supported by the Nature Genetics Editorial (2000), and by Baer et al. (2013), Bamshad et al. (2003), Caspari (2009), Cooper et al. (2003), Hunley et al. (2009), Jacquard (1982), Jordan (2008, Chapters 5 and 6), Keita et al. (2004), Lee et al. (2008), Livingstone (1962), Long et al. (2009), Mersha and Abebe (2015), Patrinos (2004), Romualdi et al. (2002), Rose (2009), Rotimi (2004), Schwartz (2001), Templeton (2012, 2013), Wolpoff (2009), and Yudell et al. (2016). The famous website of the Public Broadcasting Service (PBS, 2003; http://www.pbs.org/race/000_General/000_00-Home.htm) should also be consulted. Mayr (2002) claimed that race detractors were "obviously ignorant of modern biology," which is certainly not the case of the authors listed above. None of them denied that the human species was genetically diversified and that this feature should be taken into account, in biomedical research in particular. However, they believed that the biological concept of race is meaningless. Now, as we will see, the precise target of these race detractors needs to be clarified

in light of the definition of race considered. The notion that human races do not exist has now largely spread out of the scientific community. As an example, the French National Assembly voted on May 16, 2013 to withdraw the term race from all legal texts. One of the definitions of race given by an edition of the Larousse dictionary (2009) goes without comment: "Category of biological classification and of hierarchization of the various human groups, *scientifically aberrant* (my emphasis), whose use is at the origin of the various racisms and their practices." Would the "absolute paradigm shift" recommended by Goodman (2003) therefore be on the way?

Other scientists still do not adhere to this notion. They consider that race is a reliable biological entity and find it a useful proxy, especially for medicine and biomedical research. Contemporary scientists who consider the concept of race as meaningful and informative are Bustamante et al. (2011), Dobzhansky (1962a, 1973), González Burchard et al. (2003), Harpending (2002), Huston and Raymond (2013), Jorde and Wooding (2004), Mayr (2002), Mountain and Risch (2004), Risch et al. (2002), Shiao et al. (2012), Tate and Goldstein (2004), Tishkoff and Kidd (2004), and Woodley (2010). However, some of these scientists avoid the term race, or use careful quotation marks for it. Of course the supporters of race-based IQ differences use the concept of biological race (Arvey et al., 1994; Herrnstein and Murray, 1994; Rushton and Jensen, 2006). So do several recent popularizations (Cochran and Harpending, 2009; Leroi, 2005; Sarich and Miele, 2004; Wade, 2015). It is therefore untrue to state that there is consensus on the "absolute paradigm shift" (ie, race = biological myth), or even that this is a dominant view in the scientific community. A 1985 survey proposed the following statement to a variety of scientists: "There are biological races within the species *Homo sapiens*." Among PhD-granted biologists, 73% agreed, 15% were neutral, and 22% disagreed. Among PhD-granted physical anthropologists, the figures were 50%, 7%, and 42%, respectively (Lieberman et al., 1992). Now, in both the race detractors' and race realists' camps (Malik, 2012), the precise meaning of race must be clarified.

What Are We Talking About?

If we consider the many different meanings of the biological concept of race, the main ones are as follows: (1) races are typologically defined, that is to say, they are clearly differentiated from each other, with sharp boundaries, and there is little variation around an ideal type characterizing each of them; (2) races are phylogenetic lines (phylogeny is the science that retraces the evolutionary history of organisms): they are defined as distinct evolutionary units, characterized by more or less demanding phylogenetic criteria; (3) races are subspecies or geographic races. The typological concept is often presented as the lay definition of race. However, I am not sure this has been verified. It would seem that there is no unified folk/lay concept of race. Authors who speak about this folk concept may omit to define it (Pigliucci, 2013). The phylogenetic concept is used in conservation biology (Avise and Ball, 1990; Avise, 2000, 2004; Templeton, 1999, 2013) and to my knowledge, it has not been traditionally applied to human populations in the past. The subspecies concept has been the classic view of zoology, population genetics, and physical anthropology (Mayr, 2002; Dobzhansky, 1962a, 1973; Hooton, 1926; Vallois, 1976).

Typological

The typological concept of race ("essentialist" or "classic") is the most frequent target of race detractors. This was the case for the 1998 AAA statement ("human populations are not unambiguous, clearly demarcated, biologically distinct groups"); the race concept presented by Gravlee (2009); Jacquard, Jacob, and Ruffié (cited by Taguieff, 1988); Jordan (2008, Chapters 5 and 6: "the idea of race *in its most extreme form*" [my emphasis]); Klarsfeld and Vernier (1998: "modern genetics has refuted the idea, so widespread no more than a few decades ago, of a fundamental division between great races, of clearly distinct biological essences"); Ousley et al. (2009); Relethford (2009: "the boundaries in global variation are not abrupt and do not fit *a strict view* [my emphasis] of the race concept"); and Yudell et al. (2016: "commonly defined racial groups are genetically heterogeneous and lack clear-cut genetic boundaries"). However, as Mayr (2002) emphasized, this typological race concept has long been abandoned in anthropology. It may therefore be counterproductive to continue to attack this outdated concept. Incidentally, it should be noted that describing types does not imply that variation around the types is to be neglected. Classic species descriptions are still based on the thorough analysis of a "type" specimen, which is deposited in a national reference museum, where specialists are able to analyze it. However, modern taxonomists are perfectly aware that many species are highly variable.

Phylogenetic

The phylogenetic race concept has been defined by Avise and Ball (1990) as follows: "subspecies are groups of actually or potentially interbreeding populations phylogenetically distinguishable from, but reproductively compatible with, other such groups. Importantly, the evidence for phylogenetic distinction must normally come from the concordant distributions of multiple, independent, genetically-based traits." The use of phylogenetic criteria frequently leads to rejecting the idea that human races have

a biological reality (Keita et al., 2004; Templeton, 1999, 2013). As a population geneticist, I have always been slightly puzzled at the use of a phylogenetic concept, or at least, too strict a use of it, for races or subspecies. Since by definition races feature no genetic isolation mechanisms (unless they correspond to nascent species: "species in statu nascendi"; Dobzhansky and Spassky, 1959) and have been genetically isolated by geographical separation only, problems recognizing them through phylogenetic criteria are not unexpected. As noted by Cracraft (1983), subspecies (races) cannot have an ontological status as evolutionary units under the phylogenetic species concept. I see phylogeny as a useful criterion for characterizing subspecies, for making clear that they indeed have no strict limits, and for clarifying their characteristics (degree of divergence, demographic history, phylogenetic character mapping; see Chapter 6). However, relying on this criterion to reject in absolute terms the biological concept of race, especially when settling demandable quantitative thresholds of divergence (Templeton, 2013), seems debatable. Such a criterion of divergence threshold is not even used in the phylogenetic species concept, which states only that "a species is the smallest diagnosable cluster of individual organisms within which there is a parental pattern of ancestry and descent" (Cracraft, 1983). A telling case of the difficulties of using phylogenetic criteria in taxonomy involves pathogenic microorganisms. As a rule, clones, strains, and even species of bacteria and parasites exhibit imperfect genetic isolation. In spite of in-built biological mechanisms inhibiting genetic exchange among them, occasional mating, hybridization, and horizontal gene transfer are observed even among different species of microbes. Strict cladistic demands therefore are not operational in their characterization. Still the fact remains that clones, strains, and species are a biological reality and need to be individualized for taxonomical and medical purposes. A flexible phylogenetic analysis with relaxed criteria is the adequate means to address the question (Tibayrenc and Ayala, 2012). Fuzzy limits among clones, strains, and species of microbes on one hand, and among human populations on the other hand, obviously do not have the same evolutionary cause. I am taking this analogy for comparison purposes only, to illustrate the view that in both cases, a flexible phylogenetic approach is a more adequate tool than classic cladistic analysis. If such a relaxed phylogenetic method is adopted, human races can fit the phylogenetic race concept as defined by Avise and Ball (1990).

Subspecific

The subspecies race concept is common to population genetics, zoology, and physical anthropology. It is at the antipodes of a typological approach of the question. Indeed, the subspecies concept rejects the existence of strict boundaries between races and of genetic homogeneity within them. Although concepts and definitions are not the same in zoology, population genetics, and physical anthropology, they overlap substantially, and the common denominator is strong.

The zoological concept of subspecies remains relevant, since it is included in the international code of zoological nomenclature (Lherminier and Solignac, 2005). A subspecies is given a triname, for example, *Bos taurus primigenius* (the wild ox: aurochs). The zoological definition of subspecies is classically based on phenotypic characters and on the 75% criterion (Amadon, 1949), which states that 75% of the individuals of a population must be separable from all (100%) individuals of overlapping populations before granting subspecies status. The criterion retained is therefore a statistical one. It does not demand that 100% of the members of subspecies A be distinguishable from 100% of the members of subspecies B. Mayr (2002) gave the following definition: "I define a 'geographic race' or subspecies as 'an aggregate of phenotypically similar populations of a species inhabiting a geographic subdivision of the range of that species and differing taxonomically from other populations of that species.'"

Where population genetics is concerned, Dobzhansky (1962a, 1973) indisputably viewed human races as subspecies. This author defended the notion that subspecies represented not only taxonomical units, but also Mendelian, evolving populations, with no genetic or phylogenetic boundaries separating them. It is untrue to state that "His transformation from defender to detractor of the race concept in biology still resonates" (Yudell et al., 2016). It is worth citing the very statements of the author: "It does not follow that races are arbitrary and 'mere' inventions… Race differences are facts of nature which can… be ascertained objectively" (Dobzhansky, 1962a: p. 268); and: "It is the contention of a small but vociferous group of students that mankind is not differentiated into races… I believe [this contention] is not [justified]… Mankind is not homogeneous or uniform. The diversity would still have to be described, studied, and explained" (Dobzhansky, 1973: p. 52; published only two years before the author passed away). Even if Dobzhansky's concept of race as subspecies considerably evolved over time (Gannett, 2013), to my knowledge, he never explicitly rejected it. Hartl (1985) gave this evocative image of the population genetics concept of race: "By way of analogy, the human gene pool is composed of a number of smaller pools—puddles—like the water puddles on a gravel street after a heavy rain, all interconnected in tiny rivulets through which material flows from one to the next. If one examines the puddles closely, one sees that they are not identical… But the differences are quantitative, not qualitative. The puddles are distinguished by how much or how little they have of each component

and not by whether or not they possess the constituent. No puddle is completely isolated, so whatever one puddle has in abundance travels through the rivulets to the others. Because of this structure, the puddles form one large, interconnected unit, but a unit with local differences. The puddles in the analogy represent races—groups whose allele frequencies differ from those of other groups." Ayala and Kiger (1984) insisted on the necessity of defining races based on the frequency of many loci: "races are populations that have somewhat differentiated *gene pools*. The differences among races must involve the gene pool as a whole, and therefore allelic frequencies at many loci. Differences in one locus or trait may serve as indicators of overall genetic differentiation, but alone, they do not constitute a sufficient fundament for distinguishing among races." King & Stansfield's Dictionary of Genetics (1990) gave the following definition for race: "a phenotypically and/or geographically distinctive subspecific group, composed of individuals inhabiting a defined geographical and/or ecological region, and possessing characteristic phenotypic and gene frequencies that distinguish it from other such groups. The number of racial groups that one wishes to recognize within a species is usually arbitrary but suitable for the purposes under investigation."

Lastly, as noted above, physical anthropology has long discarded typologism. As early as 1926, Hooton fully recognized the great variability of each racial type, although he insisted on the necessity of describing types (as species describers still do). Vallois (1976) described all possible intermediary populations, races and subgroups in detail within the so-called *grand'races*. This author therefore cannot be accused of typologism, and by the way, of racism either (Bocquet-Appel, 1996). According to HoSang (2014), Coon defined races as "breeding populations" and embraced the idea of geographically defined human subspecies differentiated in part "by molecular differences in their regulatory genes."

So, What Is the Target?

Race detractors, as described above, concentrated their critiques on the typological race concept, or, to a lesser extent, on the phylogenetic race concept. The subspecies concept of human races, which has been the dominant view in zoology, population genetics, and physical anthropology for a long time, was much less attacked. As a broad angle of attack, some race opponents opted for a general criticism of the concept of subspecies in general, within which human races would be no more than a particular case. It is true that many evolutionists and geneticists consider that the subspecies is a problematic taxonomic category, amounting to a mere classification entity that cannot be considered as an evolutionary unit. In his seminal article on the nonexistence of human races, Livingstone (1962) noted that increasing numbers of scientists were dissatisfied with the general concept of subspecies in zoology. Its limitations, according to him, should be extended to the human subspecies or races. When Yudell et al. (2016) state that "phylogenetic and population genetic methods do not support a priori classifications of race, as expected for an interbreeding species like *Homo sapiens*," this implies that the criticism can be extended to any interbreeding species, and therefore, that the subspecies concept is invalid for any species. Retaining the general concept of subspecies in taxonomy is really a matter of personal convenience. Any reasonably trained zoologist knows that subspecies exist. They are the joy of carabid and cetonid beetle collectors. Are they relevant taxonomic or evolutionary units? Each scientist can decide for him- or herself. In taxonomy, there are "splitters" (who enjoy describing many tiny taxa) and "lumpers" (who prefer big, fat taxa). It is mainly a matter of tradition. What seems clear is that major geographical human populations have neither a typological structure nor sharp boundaries and they cannot resist an excessively drastic cladistic assault. However, they do not clash with the phylogenetic subspecies concept, if this is applied with flexible criteria with no divergence threshold, and with the subspecies concept used in zoology, population genetics, and classical anthropology. Phenotypically, they easily fulfill the 75% criterion (Amadon, 1949). Allele frequency differences among them are correlated (Edwards, 2003), which fulfills the criteria proposed by Avise and Ball (1990) and Ayala and Kiger (1984). Other parameters under debate (*F*st, discreteness) will be presented in greater detail in the next section.

So, Do Races Exist?

Long and Kittles (2003) stated: "Surprisingly, a great deal of variation within groups is compatible with biological race concepts [i.e., essentialist, populational, taxonomical, lineage-based] and therefore partitions of genetic variation such as those achieved by simple statistics such as *F*st do not provide critical tests for the existence of races as defined by biologists. Four decades ago, Frank Livingstone declared the nonexistence of human races (Livingstone, 1962). It is now time for geneticists and anthropologists to stop worrying about what does not exist and to discover what does exist." Later, Long et al. (2009) criticized the biological concept of race according to other criteria (clustering hierarchization). To decide whether or not races exist is largely a matter of definition, criteria selection, and semantic strategy. The decision between "yes" and "no" is all but self-evident and cannot receive a final, cast-in-stone answer. Let us consider some additional debates that will help shed light onto the controversy.

IS RACE A SOCIAL CONSTRUCTION?

It undoubtedly is. Having worked close to 20 years in various parts of the world (Algeria, French Guiana, Bolivia, Thailand, the United States), my personal experience is that the perception and status of races around the world is eminently variable. However, the *identification* of races does not vary that much. When major geographical groups are considered, there are no huge discrepancies between their classification given by Linnaeus (1758: Africanus, Americanus, Asiaticus, and Europeanus), the slightly more detailed one by Blumenbach (1806; cited by Vallois, 1976), Vallois' *grand'races* (1976), and the major continental groups revealed by modern molecular markers (Rosenberg et al., 2002, 2005). Vallois mistakenly classified Melanesians with Africans, misled by a phenomenon of phenotypic convergence (possession of similar characters in different groups not caused by common ancestry, but rather, by convergent evolutionary pressures, like flippers in dolphins and fishes). Apart from that, his *grand'races* fit the major continental groupings. Even the imperfect legal categories of the US census and the somewhat confusing ones given by the US Centers for Disease Control ("African American," "Black," "Latino," "Hispanic," "Asian" "Asian American," "Native American," "American Indian," "Alaska Native," "Native Hawaiian," "Pacific Islander," and "minority"; Burchard et al., 2015) are far from being totally disconnected from these groupings. There is something robust in these recurrent major classifications. How many subdivisions should be distinguished within these major groups is another story (see the section, "So, How Many Races (If Any)?").

Social Constructions or Models?

HoSang (2014) argued that "the observer and not the observed declares which differences constitute a racial group and which do not." This is beyond any doubt. However, the same can be said about any taxonomical effort. It is the observer, not the observed living world, who decides which (difficult and changing) criteria should be used to define species. It is the physician who decides what should be called "malaria." Traditional societies of Africa, according to my anthropologist colleagues, have a different vision of what "malaria" is. For these societies, each symptomatic form is a different disease, with a specific name. It is our knowledge of the causative agent *Plasmodium* spp. that led us to build a single, etiological framework for the disease. I would say that, as a social construct, human races appear to me less disputable than most psychiatric symptomatologic frameworks (see Frances, 2013). Psychiatric illnesses have fuzzy boundaries and no pathognomonic symptoms (signs that allow the diagnosis of a disease without any doubt). However, the identification of mental disorders is crucial for their treatment. Similarly, the classification of autoimmune disorders is a headache, with much social construction, hypothetical etiologies, and few (if any) clear-cut boundaries: dermatomyositis, Sjögren's syndrome, systemic lupus, scleroderma, and vasculitis have overlapping symptoms in some cases. Physicians are used to handling imperfect, unclear categories. The art of medicine is well versed in making decisions with the information at hand and cannot afford to wait for ideal concepts. Science, especially biomedical research, is not the passive contemplation of a magma of uninterpreted rough data. It is indispensable to describe categories, even if they are not 100% satisfactory. There is nothing worse than saying that categories are imperfect, hence we know nothing. One cannot make do without models. What HoSang (2014) actually states amounts to saying that human races are only models. However, this is the same for virtually all entities conceived by the human mind, chiefly including, as we have seen, pathological classifications. We are able to describe and manage the external world only by designing the least flawed possible appropriate models. Similarly, when Morning (2014) states that the STRUCTURE model and principal component analysis (computer-based approaches used to visualize genetic variability in populations) are "statistical artifacts, shaped by researchers' techniques and assumptions," the same can be said from any scientific means of analysis, except crude visual observation. It is desirable to design models with as few a priori working hypotheses as possible. This is definitely the case for the unsupervised approach of STRUCTURE.

A Complex Interplay Between Social Construction and Biology

Human races are certainly not self-evident biological models, even if common sense and everyday experience seem to suggest it. One is able to give them solid grounding in science only with considerable scientific inquiry. Moreover, different ancestries are by no means neutral from a sociological point of view. It is clear that the very biological nature of ancestries is strongly influenced by the social constructs we build around them, consciously or not. Eberhardt (2005) hypothesized that differences in neuroimaging and neurofunctioning between "blacks" and "whites" (the terms used by the author) were probably due to the different social experiences of the two groups. These social experiences profoundly differ. In most, if not all, multiracial societies, in spite of economic progress and goodwill policies such as affirmative action in the United States, all things being equal, there still is a correlation between ancestry and socioeconomic status. This has a strong impact on the lifestyle and life quality of

populations: general education, access to health care, diet, and disease transmission, with important biological consequences. A problem I know well is Chagas disease in South America. It is caused by a parasitic protozoan and transmitted by blood-sucking true bugs, which proliferate in precarious habitats. Chagas disease therefore principally rages in poor suburbs and villages, which parallels the ancestry-based socioeconomic segregation of most Latin American countries. Similarly, transmission of tuberculosis is obviously related to socioeconomic conditions, even if the genetic diversity of humans and the pathogenic agent plays a role, as is the case for all transmissible diseases. Tuberculosis, AIDS, and malaria have been identified as the three primary transmissible "diseases of poverty" by the World Health Organization. Economic differences and health care disparities are not the only negative experiences some minorities encounter. Despite all official antiracist policies, discrimination, or at least unspoken apartheid, continues in all multiracial societies. Such sociological barriers limit the number of interracial marriages, which reinforces the genetic isolation among groups of different ancestries (endogamy) and hence impacts the biological background of different human groups. The percentage of mixed marriages between European Americans (EURAs) and African Americans (AFAs) in the United States according to the 2000 census was 0.3% in EURAs and 4% in AFAs (Ousley et al., 2009) only. Sociological reasons are possibly not alone in explaining this phenomenon, since biological homogamy (the tendency to select a mating partner exhibiting phenotypic similarity: tall with tall, short with short) could interfere. However, culture, tradition, socioeconomic status, and color prejudice are most probably the main barriers against mixed marriages.

Races are social constructs, with important sociological consequences. However, genetic differences among human populations are indisputable. Actually, scientists who totally deny these differences and their possible impact on health are probably the exception rather than the rule. But many of them are reluctant to apply the biological concept of race (again not self-evident) to these differences. Close collaboration between social scientists and biologists is therefore more than ever necessary to perfect our view (model) of human diversity.

THE *F*st ARGUMENT

To make a long story short, *F*st (see Chapter 6) is a statistical measurement of genetic differences among populations. As explained in Chapters 6 and 10 and earlier in this chapter, most genetic variation in humans is observed within major geographical populations. The difference among major groups is 5−15% only (Lewontin, 1972). This has been taken as a strong argument by race opponents to state that differences among geographical groups were "relatively trivial" (Cavalli-Sforza, 2007). The rough figure itself, corroborated by various population samplings and many genetic markers, is indubitable. The interpretation is more questionable.

A strong criticism was made by Edwards (2003: "Lewontin's fallacy"), who observed that *F*st considers each genetic locus individually as if the loci were independent of each other, while those loci that show differences among populations are correlated (their polymorphisms go in the same direction). This explains why population differences can be visualized under the form of clusters and trees (Chapter 6, Figs. 6.1−6.4). Adding more genetic loci to the sample increases the accuracy of classifications, while it has minimal effects on *F*st: "The more loci there are in the data set, the more of these correlations there are, and the more information is ignored by *F*st" (Jorde and Wooding, 2004).

Another remark to be made is that phenotypic expression is not an election by universal genetic suffrage. A few genes or even only one can play a major role in some phenotypes, as can nongenic regulatory mechanisms (see Chapter 6).

Moreover, the markers used to characterize populations and compute *F*st statistics are "neutral" markers, that is to say, they are assumed to not undergo natural selection. This is a requirement for establishing reliable genealogies among ancestral groups. By their very nature, these neutral markers have no direct impact on phenotypic expression, as noted by some race detractors themselves (Cooper et al., 2003; Fujimura et al., 2014: "we stress that most of these markers are not in protein encoding genes, so it is unclear whether they are important for any phenotypic outcomes"). So the fact that only a minority of these neutral markers have different frequencies among geographical groups has no predictive value in terms of the phenotypic differences among these groups. *F*st among neutral markers is low, while *F*st measured for phenotypic variation may be much higher. For skin pigmentation, it is 0.6−0.9 (Harpending, 2002; Relethford, 2009). *F*st for loci that undergo natural selection also tends to be much higher than *F*st for neutral markers. This discrepancy is actually a classic approach for detecting such selected loci (Cavalli-Sforza and Feldman, 2003).

*F*st cannot be considered an absolute measure of evolutionary divergence. It is strongly influenced by several parameters, in particular the founder effect (when a population is founded by a limited number of individuals that harbor only a fraction of the total genetic diversity of the species), population size, and degree of isolation. Moreno-Estrada et al. (2014) found that the *F*st between two Native Mexican populations (0.132) was higher than the *F*st between Europeans and Chinese populations surveyed in the HapMap (Haplotype Map) project (0.11). However, there is no doubt that native Mexicans share

more recent common ancestors than Europeans and Chinese do. Similarly, in the parasitic species *Plasmodium falciparum*, the agent of the most malignant form of malaria, *F*st between two populations of Western Cambodia far exceeds the *F*st between Thailandese and Ghanaian populations, again due to a drastic founder effect in Cambodian populations of the parasite (Miotto et al., 2013).

Lastly, *F*st values were mostly computed from common variants (CVs; frequency, ≥5%). This misses a significant proportion of LFVs (frequency between 0.5% and 5%) and even more, RVs (frequency below 0.5%). Modern genomics has revealed that LFVs and RVs were more abundant than CVs and tended to be population-specific, in proportion to their rarity. Even when the general *F*st is low, 17% of LFVs are found in only one ancestral group. For RVs, the figure is 53% (The 1000 Genomes Project Consortium, 2012). Moreover, it is hypothesized that the role of LFVs and RVs in recent local adaptation is considerable (see Chapter 6 and "Human Genetic Diversity in Light of Modern Genomics" in this chapter). All these important features concerning LFVs and RVs are missed by current *F*st analysis.

The classic assertion (PBS, 2003), elaborated from the *F*st debate, that any two individuals from the same continental group may be genetically more different than two individuals from two different groups, is not statistically verified. This can happen in individual cases, like the story of Watson's DNA sequence being closer to an Asian sequence than to Craig Venter's sequence (Mersha and Abebe, 2015). However, a sample size of three is statistically inadequate. Some outsider Pygmies might be taller than a few, very short Swedish. This is the exception that proves the rule: "We recognize that individuals of two different geographically defined human populations are more likely to differ at any given site in the genome than are two individuals of the same geographically defined population" (Lee et al., 2008).

It can be concluded that, while low *F*st values among major geographical populations are an important population genetic feature, this cannot be considered as a final criterion to reject in absolute terms the biological concept of race (Long and Kittles, 2003).

DISCREPANCIES?

A central argument by Livingstone (1962) to counter the concept of race, also used by the website of the Public Broadcasting Service (PBS, 2003), was the non-concordance between characters, an argument amply used by Jacquard (1982) as well. If one considers one character, for example skin color, one obtains a given classification of human groups. If a second character is used, such as lactase tolerance (this means that adults are able to digest milk), a second, different classification emerges. If a third character is taken, for example, human leukocyte antigen (HLA) polymorphism (a set of genetic traits involved in immune defenses), a third classification is obtained. However, this reasoning is not valid. Subspecies have never been defined based on isolated characters, but instead on a conjunction of characters considered as a whole (see "What Are We Talking About?" in this chapter). Subspecies can be identified by one remarkable trait once their subspecific status has been recognized on a range of characters. Even the examples cited by Jacquard (1982) are not 100% discordant and show some correspondence. Among people of a given skin color (incidentally, a phenotype that has never been used in isolation to scientifically define human groups), the frequency of lactase persistence is not random. This adaptive trait is prevalent in people of European ancestry (mainly northern Europe) and in some African pastoralist populations, and virtually absent in other populations. HLA polymorphism differs widely among ancestry groups, so it will not be the same in white-skinned people as in dark-skinned people. Similarly, skin color, eye color, hair texture, cranial morphology, blood group frequencies, and genetic polymorphisms are not independent of each other. When all characters are considered jointly (not in isolation or in pairs), the evidence for a given ancestral origin increases. It is astonishing that numerical taxonomy, which stems from classifications based on as many randomly selected characteristics as possible (Sneath and Sokal, 1973) has not been used, to my knowledge, for the study of human diversity.

HOMOGENEITY AND BOUNDARIES

Major continental groups are by no means homogeneous. As discussed in Chapter 6 and at the beginning of this chapter, they are highly diversified and stratified, with a Russian doll structure. This heterogeneity is due to geographic distance and geographic obstacles, but also to cultural barriers, among which language plays an important role (Cavalli-Sforza et al., 1992; Longobardi et al., 2015). Moreover, the high genetic heterogeneity of most present populations is the result of complex passed admixtures (Hellenthal et al., 2014). This pattern could be called "the Gobineau's nightmare." Indeed, for Arthur de Gobineau (1853), one of the fathers of racist thought and the Aryan myth in Europe, crossbreeding (*métissage*) was the main source of human decadence. This thorough admixture pattern fits the early view of Hooton (1926) that "secondary races" (resulting from long-continued intermixture of two or more primary races within an area of relative isolation) constitute most of the present population of the world.

As we have seen, there are no strict boundaries among the main continental groups, which show clear overlapping. This is a commonplace and expected pattern for

geographical races/subspecies (Malik, 2012). It can even be observed in the case of true species through the "ring species" phenomenon (the situation in which two populations that do not interbreed live in the same region and are connected by a geographic ring of populations that can interbreed). There are many cases in which different "species" have fuzzy boundaries. Examples are numerous in triatomine bugs, the blood-sucking true bugs that transmit Chagas disease in Latin America (Lent and Wygodzinsky, 1979). As explained above, there are many examples of bacterial species that have fuzzy boundaries (Tibayrenc, 2006). Genetic exchange can even be observed between bacteria from different genera, such as *Escherichia coli* and *Salmonella*. As we have seen, genetic heterogeneity and fuzzy limits allow one to reject the typological concept of race. However, they do not argue against either the phylogenetic or the subspecies concepts.

Fuzzy boundaries are the rule rather than the exception in the material world. In medicine, physicians settle limits that are assumed to separate the normal from the pathological. Some people who are beyond the cholesterol level limit defined as normal will be healthy, while other people within these limits will suffer from the symptoms of hypercholesterolemia. Setting such limits is always somewhat arbitrary.

There are no strict limits between day and night, childhood, adolescence, adulthood, and old age, between the colors of the spectrum (Klarsfeld and Vernier, 1998). We use a rich vocabulary to describe the many intermediary states in these categories: dawn, dusk, early childhood, youth of old age, blue-green, yellow-orange, and so forth. However, dawn does not become day in a given fraction of a second, and an adolescent does not become an adult in a snapshot. The analogy between these categories and human populations is all the more true when they do not show perfect continuums (except the color spectrum). There is not a continuous increase and decrease of light during the day. The increase and decrease accelerate when the sun rises and sets. Aging progresses by crises (puberty, menopause). Similarly, genetic and phenotypic variation in human populations at the scale of the whole world do not fit a perfect continuum if populations are randomly selected. In response to the famous statement by Livingstone (1962) that "there are no races, there are only clines," Dobzhansky (1962b) stated that these clines were not uniform. Some clustering, mainly due to major geographical obstacles (the Sahara, oceans, the Himalayas) is apparent in worldwide populations (see Chapter 6 and Rosenberg et al., 2005): "Our evolutionary history is a continuous process of combining the new with the old, and the end result is a mosaic that is modified with each birth and death. This is why the process of using genetics to define 'race' is like slicing soup: 'You can cut wherever you want, but the soup stays mixed'" (cited by Rotimi, 2004). This is a pleasant metaphor. However, (1) the human soup is somewhat lumpy; (2) humankind is not homogeneous like soup. Even if human populations were perfectly clinal, which is not a consensus view, and is the object of a fundamental disagreement among physical anthropologists (Edgar and Hunley, 2009), it would be informative to slice it up into a limited number of units of analysis, as we do for the spectrum of colors: nobody thinks about describing millions of different colors.

SO, HOW MANY RACES ARE THERE (IF ANY)?

This is a recurrent question and a widely used absurdum argument of race opponents (Foster, 2004; Foucart, 2013). For argument's sake, let us accept the concept of races as subspecies or fuzzy phylogenetic lineages: how many of them should we count? The high structuration and Russian doll pattern of human populations, together with the power of modern genetic markers, make it possible to delimit an infinity of tiny clusters at the local level, for example among British populations (Leslie et al., 2015). Malik (2012) has poked fun at the extreme view that the inhabitants of Ithaca and Albany, New York, could be considered as pertaining to different races. Dobzhansky himself was in trouble for giving a final answer to this conceptual difficulty. His concept of race as subspecies considerably evolved over time (Gannett, 2013). However, he clearly stated that "race differences are objectively ascertainable biological phenomena, and discovery of races is a biological problem, while naming them is a nomenclatorial problem. Whether races should or should not be named, and if they should, how many should be recognized is a matter of convenience and hence, of judgment" (Dobzhansky, 1962b). Given the widespread mini-clustering of human populations, it is easily understandable why anthropologists described highly variable numbers of races. This is a mere matter of "splitters and lumpers." Human races are not the only case of nomenclatorial quandary. As I have already detailed, micropathogens also have a Russian doll structure (whose evolutionary cause is quite different from that of human Russian dolls). *Trypanosoma cruzi*, the parasite responsible for Chagas disease, is clearly subdivided into six major genetic clusters. Some "splitter" colleagues of mine are eager to equate them with true species. It is apparent that some of these clusters are themselves subdivided into lesser clusters. Shall we make new species with these microclusters, and propose that Chagas disease is caused by 20 or 30 different species? It would be as absurd as the story about Ithaca and Albany species. The case of *T. cruzi* is not unique, since many pathogen species exhibit the same Russian doll pattern (Tibayrenc and Ayala, 2013).

Tradition and relevance play important roles in describing human races. We have seen that the concept of four to five major continental groups has been repeatedly proposed since Linnaeus' classification (1758). The groups that emerge from modern genomic data are "more or less the major races of traditional anthropology" (Leroi, 2005) and "generally correspond to socially recognized races" (Tishkoff and Kidd, 2004). Vallois (1976) distinguished a total of 27 races under his *grand'races*. There is in fact no final answer to the question of the number of races. All depends on the question under study, the goals of the observer, and the level of resolution required. In many instances, major continental groups are the proxy retained. For example, in the United States, many studies compare AFAs versus EURAs. In the multiracial American society, history joined "the most extreme human phenotypes (Western Europe, West Africa, and East Asia)" (Edgar, 2009). The HapMap genomic project (http://hapmap.ncbi.nlm.nih.gov/) retained this minimal sampling scheme of the "extreme human phenotypes" (Africans, Europeans, and Asians). Its sampling has been used by many teams. However, since recent local adaptation appears to be a major feature of human evolution, where disease study is concerned, approaching populations at a much finer level than the major continental groups may be necessary. A striking example is the Fulani, a pastoralist people of West Africa who exhibit a strong resistance to malaria compared to other groups (the Mossi) who live in the same areas (see Chapter 10). The biomedical relevance of considering lesser populations within major continental groups does not mean that all tiny human groups should be given a race name. Doing this could be quite confusing.

RACES, SUBSPECIES, AND SPECIES IN ANIMALS

As stated in the introduction, it is relevant to draw comparisons with other species to better evaluate the taxonomical status of human populations.

Dogs come in a wide range of breeds, which are the result of centuries of targeted selection by breeders. Recent natural selection in humans appears to have mainly operated on standing variation (ie, existing variation rather than new mutations), polygenic characteristics, and regulatory phenomena (see Chapter 6). This means that it can be compared to a large extent to the artificial, purposeful selection undertaken by dog breeders, which acts through similar mechanisms. Dog breeds have been selected not only for their external phenotype, but also for behavioral characteristics, which can differ greatly from one breed to another (Sarich and Miele, 2004, Chapter 8). Dog breeds also differ in their drug sensitivity (Sarich and Miele, Chapter 7). Contrary to what Jordan (2008, Chapter 10) states, dog breeds are not "extremely homogeneous" with most genetic differences among breeds rather than within breeds. Within-breed and between-breed genetic differences (for common, neutral markers: see "the *F*st argument") are 65% and 35%, respectively (vonHoldt et al., 2010). Even if within-group human genetic diversity is higher, the dog pattern reflects the main tendency, namely that most genetic diversity in dogs is within the breeds, not between them. This confirms that the *F*st argument (see earlier in this chapter) says little about phenotypic differences among populations. As taunted by Cochran and Harpending (2009) in their Chapter 1, the *F*st argument used for human populations applied to dogs would lead to considering that two Great Danes might exhibit more differences than a Great Dane and a Chihuahua.

Subspecies have been described in apes. Templeton (2013) stated that the race concept was valid in chimpanzees, while it was not in humans. This is again a matter of definition and criteria. The criterion used here was a threshold of a phylogenetic divergence of 25% among races, obviously not fulfilled by major human continental groups. However, Fischer et al. (2006) noted that levels of sequence divergence and genetic differentiation among chimpanzee and orangutan subspecies was comparable to that seen among human populations. The authors noted that morphological differences among ape subspecies were small and hard to define (which is not the case for human continental groups). Contrary to Templeton (2013), they concluded by questioning the validity of the subspecies concept in these apes. Still the fact remains that these ape subspecies have been described and validated.

Woodley (2010) stated that the observed heterozygosity (a measure of genetic heterogeneity) among human populations was greater than that of many described animal subspecies.

The zebu and the polar bear constitute two informative cases for comparison purposes. For a very long time, the zebu, which is perfectly interfertile with the European ox, has been considered a distinct species (*Bos indicus*). It is only recently that it lost its species status. It is nevertheless considered a full subspecies (*Bos taurus indicus*), although many intermediary phenotypes exist between *Bos taurus taurus* (the European ox) and *B. taurus indicus*. The polar bear is classified as a species (*Ursus maritimus*), distinct from the brown bear (*Ursus arctos*). However, the two species produce fertile offspring, including now in nature ("pizzly"; Vincent, 2010). This is assumed to be explainable by global warming, a consequence of which being that the two species coexist in some areas. Polar and brown bears are genetically closely related, according to both nuclear and mitochondrial genes (Yu et al., 2004). In mitochondrial-based phylogenies, polar bears appear as a subdivision of brown bears. Alaska brown bears are genetically closer to polar bears than to other geographical

populations of brown bears. This might suggest that the polar bear is only a recently appeared subspecies of the brown bear, whose phenotypic specificity may be due to strong selective pressures undergone in extreme climates (Avise, 2004).

These two examples and the other examples cited above show that for rather comparable genetic data, various animal and human populations may be attributed different taxonomical statuses. Taxonomy is a difficult art with, quite often, considerable subjectivity and no clear-cut answers: "Nature laughs at our classifications."

SEMANTIC CAUTION: A HEADACHE

If one decides that major continental human groups, and possibly some lesser groups, fit the concept of subspecies or geographical races, should we opt for calling them "races"? The response is absolutely not self-evident. For historical reasons and continuing discrimination, the term makes many people uncomfortable, even upset: "Incidentally, I am inclined to dismiss the word 'race' because of its connection with the odious episodes of racism with which we are continuously confronted" (Cavalli-Sforza, 2007). Jacquard (cited by Taguieff, 1988) recommended "eliminating the term of race as a useless and dangerous tool."

As I have mentioned, many researchers who cannot be suspected of racism (Dobzhansky, 1962a, 1973, among others) do not hesitate to use the term "race." According to Dobkzhansky (1962b), "to say that mankind has no races plays into the hands of race bigots." Many other authors nevertheless prefer to use cautious euphemisms, even if the concept they have in mind may be close to the subspecies concept defended by Dobzhansky (1962a). "Beneath the jargon, cautious phrases and academic courtesies, one thing was clear: the consensus about social constructs was unraveling. Some even argued that, looked at the right way, genetic data show that races clearly do exist. One of the more painful spectacles of modern science is that of human geneticists piously disavowing the existence of races even as they investigate the genetic relationships between "ethnic groups". Given the problematic, even vicious, history of the word "race," the use of euphemisms is understandable. But it hardly aids understanding, for the term "ethnic group" conflates all the possible ways in which people differ from each other" (Leroi, 2005). I think even more than this author that the euphemism "ethnic group" is a complete semantic disaster, since its initiator is the racist author Vacher de Lapouge. Moreover, according to the original meaning, the term refers to cultural attributes only, with no biological meaning. It is therefore a complete misinterpretation of the biological race concept. "Geographical/continental ancestry groups" was proposed by Baer et al. (2013). Jordan (2008, Chapters 2 and 14), for fear of racism but also because he considers that the term "race" is poorly defined, recommended rejecting it and instead using "ascendance" (ancestry). Similarly, Rose (2009) advised using "biogeographic ancestry," not only as a euphemism but also because he disagreed with the validity of the biological race concept. Rosenberg et al. (2005) cautiously noted: "our evidence for clustering should not be taken as evidence of our support of any particular concept of 'biological race.'" Relethford (2009) lucidly raised the question, "In cases where broad geographic groups are used, should we refer to these groups as 'races' or should we use *more politically correct* [my emphasis] terms such as 'geographic regions' or 'geographic clusters'?" It remains to be seen, however, if such semantic caution is not counterproductive among students and the public. Caulfied et al. (2009) noted that "narrowly defined terms, such as ancestry, are likely to have less public recognition than race" and that "the relevance of race and of race categories far exceeds the arena of scientific discourse and becomes the concern of government regulation, media accounts and language debate, science cannot independently dictate its meaning or invent new terms to replace it."

CENSORSHIP?

A concern of another kind may come from the possible threat to the very possibility of freely debating the question of race.

Although open to freedom of research, including for IQ racial comparisons, Ceci and Williams (2009), proposed that "perhaps such research should be forced to pass a higher cost−benefit threshold before publication." Similarly, Altshuler (cited by Richardson, 2011) called for a "higher standard of proof" for this kind of research. All this is no less than a low-level form of censorship. The temptation is strong for the referees to use a particularly high "cost−benefit threshold" (an eminently subjective criterion) or a "higher standard of proof" as alibis for simply barring the road to a kind of research they dislike. The prerequisite not to build a specific population genetics for humans should be kept firmly in mind here. Criteria to evaluate articles should be the same whatever model is used, be it *Homo sapiens* or *Triturus cristatus*. Rose (2009) considered that research on race and IQ should be discouraged ("just ideology masquerading as science"). So did Jordan (2008, Chapter 2). It is obvious that research on racial differences in intelligence and cognition constitutes a special case, with "potentially explosive implications" (Richardson, 2011). Surely circulating results about this research in the media and the public calls for utmost caution. However, the tendency toward more or less explicit censorship is not limited to cognition and IQ research and may be extended to the race debate as a whole.

According to Cooper et al. (2003), "To invoke the authority of genomic science in the debate over the value of

FIGURE 37.1 Illustrations of human diversity in the scientific literature as well as in lay productions (advertisements) still have a strong tendency to use pictures of Africans, Asians, and Europeans, traditionally described as major "races". Here, variation of facial expressions among different human populations take as key example Europeans, Asians and Africans. *After LoBue, V., Thrasher, C., 2015. The Child Affective Facial Expression (CAFE) set: validity and reliability from untrained adults. Frontiers in Psychology 5, 1532. doi: 10.3389/fpsyg.2014.01532.*

race as a category of nature is to accept the social meaning as well… The discovery that races exist is not an advance of genomic science into uncharted territory; it is an extension of the atavistic belief that human populations are not just organized, but ordered." The message is clear: scientists who rely on the biological race concept cannot ignore the social message of it. Describing races could even amount to *ordering* them. The Editorial of Nature Genetics (2000) warned that: "From now on, *Nature Genetics* will therefore require that authors explain why they make use of particular ethnic groups or populations, and how classification was achieved. We will ask reviewers to consider these parameters when judging the merits of a manuscript—we hope that this will raise awareness and inspire more rigorous design of genetic and epidemiological studies." In their "guiding principles on using racial categories in human genetics," Lee et al. (2008) proposed (statement 7) that "we discourage the use of race as a proxy for biological similarity and support efforts to minimize the use of the categories of race and ethnicity in clinical medicine." A sadly, censorship-smelling famous affair was the boycott of the Human Genome Diversity project (HGDP), which aimed at surveying the genetic diversity of "isolated indigenous people." One of the leaders of the project was Lucas Cavalli-Sforza who, in addition to being an eminent scientist is an indisputable moral authority. This did not prevent the World Council of Indigenous People (WCIP) from attacking the HGDP as a "racist, colonialist, vampire project." Reardon (2005) proposed that the project at its very start should have included social sciences, with more in-depth reflection on race and power in science. As a result of the crash at take-off of the HGDP, research on human genetic diversity continued, but the initiators of other projects avoided controversies of that kind as much as possible, without taking into account the issues related to social sciences raised by Reardon (2005).

It looks as though the recommendations of the Editorial in Nature Genetics (2000) and the above-cited authors, as well as the distressing HGDP episode, did not slow down ancestry-based research. Many recently published articles are based on compared geographical and ancestry samples (see Chapters 6 and 10). A remarkable case is the HapMap project, whose initial sampling comprised three populations: (1) the Yorubans (YRI) from Nigeria; (2) Utah residents with ancestry from northern and western Europe (CEU); and (3) the Japanese Tokyo (JPT) population plus Han Chinese in Beijing, China (CHB). In other words, this sample was based on Africans, Europeans, and Asians, three of the *grand'races* (Vallois, 1976), "the most extreme human phenotypes" (Edgar, 2009), which in addition to scientific publishing, remain omnipresent as a reference in cinema, literature, advertising, etc., every time human diversity is evoked (Fig. 37.1).

TWO DIFFERENT STRATEGIES TO FIGHT RACISM

To conclude this chapter, we will discuss efficient strategies that could be designed to fight racism.

Science-Based Antiracism

A major strategy after World War II and the discovery of Nazi crimes has been to base antiracism on scientific data. This has been called the "absolute paradigm shift" (Goodman, 2003). The goal was to demonstrate that race was a mere social construction and a biological myth. To eliminate the word or to deny its biological value was a

prerequisite for eliminating racism. If races did not exist, racism would appear inept (Taguieff, 1988). This absolute paradigm shift only partly convinced the public. As noted by Edgar and Hunley (2009), "Although we have now been teaching for generations that races do not exist, these naïve notions [typological views] persist [among students] and they continue to have social and scientific consequences." Abrupt statements such as "science gives the irrefutable proof that human races do not exist" could be counterproductive (Klarsfeld and Vernier, 1998). As for the scientific community, as we have already seen (see "The Taxonomical Problem: Are There 'Races'?"), the absolute paradigm shift is not shared by all biologists, or even by a majority of them. As deplored by the Editorial of Nature Genetics (2000): "on one hand, the public is told that there is no scientific basis for race, and that there is more variation within populations than between populations. On the other, scientists use racial terms when describing research results, such as an increased risk for breast cancer in Jews or for prostate cancer in Blacks, and frequently emphasize population-specific markers, alleles and disease susceptibility." As we have seen throughout this chapter, deciding whether "there are races" (Huston and Raymond, 2013) or "there are no races" (Livingstone, 1962) is highly dependent upon the definition used for the term and therefore cannot be provided with a final, crystal-clear response. So given this lack of consensus, even among scientists, it is illusory to hope that the absolute paradigm shift will be able to eradicate racism. It should be remembered that the first UNESCO statement on race (1951) did not deny the existence of human races and called only for equal rights for all members of humankind.

The great danger of this science-based antiracist strategy is that if science supported the existence of races, or even worse, race inequalities for cognitive ability, for example, then racism could be considered as justified. As reported by Klarsfeld and Vernier (1998), "I think a geneticist has the duty of using the discoveries he has made as a rampart against what he ideologically condemns." This risky mixture of morals and science means that the one who is right, either the racist or the antiracist, is the one who has science on his side. The danger is that science is changing. Data can be refuted, in one direction or the other. The same data can be interpreted in different ways according to the background and the psychological profile of who analyzes them. Clear-cut, final answers do not exist in science. There are no proofs, there are only working hypotheses. So if we make this issue dependent upon scientific data, antiracism would be constantly threatened by new results (which are presently pouring in), new hypotheses, new interpretations. The warning should therefore be sounded that this strategy of founding antiracism on scientific data, whatever its good intentions may be, is perilous. For example, research on brain or behavior genes is still in its infancy (Richardson, 2011; Vitti et al., 2012; Woodley et al., 2014). Its future results are today entirely unpredictable.

Morals-Based Antiracism

The opposite strategy is to decide once and for all that antiracism should be exclusively based on moral/societal choices. Morals and science should be *mutually sanctuarized*. Our moral choices should be independent of scientific data. In turn, morals should not dictate scientific conclusions, a tendency only too often observed. If a hypothesis was considered wrong every time it appeared scandalous, heliocentrism (Copernicus), the theory of evolution (Darwin), the high antiquity of man (Boucher de Perthes), and infant sexuality (Freud) would have been rejected.

We all know that there are differences (innate or acquired by education, or both) in talent, strength, size, disease susceptibility, attractiveness, etc., among people. These are crude data. Laws do not care. As a societal choice, they consider that all men and women (should) have equal rights. This is the same for populations of different ancestries. Whatever the data yielded by science now or in the future may be, people must have equal rights, equal access to health care and education, and racism must be against the law, full stop: "We emphasize that the existence of differences, however small, should not be a basis for discrimination. Statements like 'We hold these truths to be self-evident that all men are created equal…' (US Declaration of Independence, 1776) reflect morality, not science" (Tishkoff and Kidd, 2004). As Jordan stated (2008, Chapter 4), equality should not be based on biology. It is a societal choice.

The UNESCO universal declaration on the human genome (1997) should be more than enough for this morals-based antiracism and is a convenient conclusion for this chapter: "Recognizing that research on the human genome and the resulting applications open up vast prospects for progress in improving the health of individuals and of humankind as a whole, but emphasizing that such research should fully respect human dignity, freedom and human rights, as well as the prohibition of all forms of discrimination based on genetic characteristics, no research or research applications concerning the human genome, in particular in the fields of biology, genetics and medicine, should prevail over respect for the human rights, fundamental freedoms and human dignity of individuals or, where applicable, of groups of people."

REFERENCES

Amadon, D., 1949. The seventy-five per cent rule for subspecies. Condor 51, 250–258.

American Association of Anthropologists statement on race. American Anthropologist 100, 1998, 712–713.

Arvey, R.D., Bouchard Jr., T.J., Kaufman, N.L., et al., 13 December 1994. Mainstream science on intelligence. The Wall Street Journal.

Avise, J.C., Ball, R.M., 1990. Principles of genealogical concordance in species concepts and biological taxonomy. Oxford Surveys in Evolutionary Biology 7, 45–67.

Avise, J.C., 2000. Phylogeography. Harvard University Press.

Avise, J.C., 2004. Molecular Markers, Natural History and Evolution, second ed. Chapman & Hall, New York, London.

Ayala, F.J., Kiger, J.A., 1984. Modern Genetics, second ed. The Benjamin/Cummings Publishing Company, Menlo Park, California.

Baer, R.D., Arteaga, E., Dyer, K., Eden, A., Gross, R., Helmy, H., Karnyski, M., Papadopoulos, A., Reeser, D., 2013. Concepts of race and ethnicity among health researchers: patterns and implications. Ethnicity & Health 18, 211–225.

Bamshad, M.J., Wooding, S., Watkins, W.S., et al., 2003. Human population genetic structure and infererence of group membership. The American Journal of Human Genetics 72, 578–580.

Belizário, J.E., 2013. The humankind genome: from genetic diversity to the origin of human diseases. Genome 56, 705–716.

Betancourt, H., López, S.R., 1993. The study of culture, ethnicity, and race in American Psychology. American Psychologist 48, 629–637.

Boas, F., 1912. Changes in the bodily form of descendants of immigrants. American Anthropologist 14, 530–562.

Bocquet-Appel, J.P., 1996. Note sur l'origine de deux interviews: Henri Victor Vallois et Gustave Malécot. Bulletins et Mémoires de la Société d'Anthropologie de Paris 1–2, 115–124.

Burchard, E.G., Oh, S.S., Foreman, M.G., Celedón, J.C., 2015. Moving toward true inclusion of racial/ethnic minorities in federally funded studies. A key step for achieving respiratory health equality in the United States. American Journal of Respiratory and Critical Care Medicine 191, 514–521.

Bustamante, C.D., González Burchard, E., De La Vega, F.M., 2011. Genomics for the world. Nature 475, 163–165.

Caspari, R., 2009. 1918: Three perspectives on race and human variation. American Journal of Physical Anthropology 139, 5–15.

Caulfield, T., Fullerton, S.M., Ali-Khan, S.E., et al., 2009. Race and ancestry in biomedical research: exploring the challenges. Genome Medicine 1, 8.

Cavalli-Sforza, L.L., Feldman, M.W., 2003. The application of molecular genetic approaches to the study of human evolution. Nature Genetics 33, 266–275.

Cavalli-Sforza, L.L., Minch, E., Mountain, J.L., 1992. Coevolution of genes and languages revisited. Proceedings of the National Academy of Sciences of the United States of America 89, 5620–5624.

Cavalli-Sforza, L., 2007. Human evolution and its relevance for scientific epidemiology. Annual Review of Genomics and Human Genetics 8, 1–15.

Ceci, S., Williams, W.M., 2009. Should scientists study race and IQ? YES: the scientific truth must be pursued. Nature 457, 788–789.

Cochran, G., Harpending, H., 2009. The 10,000 Year Explosion – How Civilization Accelerated Human Evolution. Basic Books. A Member of the Perseus Books Group, New York.

Cooper, R.S., Jay, S., Kaufman, J.S., Ward, R., 2003. Race and genomics. The New England Journal of Medicine 348, 1166–1170.

Cracraft, J., 1983. Species concept and speciation analysis. In: Johnson, R.F. (Ed.), Current Ornithology. Plenum Press, New York, pp. 159–187.

de Praconval, M., 29 July 2009. Théorie raciale ou raciste? L'homme multidimensionnel. Le Nouvel Observateur.

Dobzhansky, T., Spassky, B., 1959. *Drosophila pardistorum*, a cluster of species in statu nascendi. Proceedings of the National Academy of Sciences of the United States of America 45 (3), 419–428.

Dobzhansky, T., 1962a. Mankind Evolving, 1962. Yale University Press.

Dobzhansky, T., 1962b. Comment on Frank B. Livingstone: "on the non-existence of human races". Current Anthropology 3, 279–281.

Dobzhansky, T., 1973. Genetic Diversity and Human Equality. Basic Books, New York.

Eberhardt, J.L., 2005. Imaging race. American Psychologist 60, 181–190.

Edgar, H.J.H., Hunley, K.L., 2009. Race reconciled?: How biological anthropologists view human variation. American Journal of Physical Anthropology 139, 1–4.

Edgar, H.J.H., 2009. Biohistorical approaches to ''Race'' in the United States: biological distances among African Americans, European Americans, and their ancestors. American Journal of Physical Anthropology 139, 58–67.

Editorial, 2000. Census, race and science. Nature Genetics 24, 97–98.

Edwards, A.W.F., 2003. Human genetic diversity: Lewontin's fallacy. BioEssays 25, 798–801.

Fischer, A., Pollack, J., Thalmann, O., Nickel, B., Pääbo, S., 2006. Demographic history and genetic differentiation in apes. Current Biology 16, 1133–1138.

Foster, M.W., 2004. Race: the reality of human differences. Journal of Clinical Investigation 113, 1663.

Foucart, S., 3 June 2013. Les "races humaines" existent? Alors énumérez-les! Le Monde.

Frances, A., 2013. Saving Normal: An Insider's Revolt Against Out-of-control Psychiatric Diagnosis, -5, Big Pharma, and the Medicalization *of Ordinary Life*. William Morrow, New York.

Fujimura, J.H., Bolnick, D.A., Rajagopalan, R., et al., 2014. Clines without classes: how to make sense of human variation. Sociological Theory 32, 208–227.

Gannett, L., 2013. Theodosius Dobzhansky and the genetic race concept. Studies in History and Philosophy of Biological and Biomedical Sciences 44, 250–261.

Gelman, A., 8 May 2014. The paradox of racism. Why the new book by the New York times' Nicholas Wade is both plausible and preposterous. Science. The state of the universe.

Gobineau, A., 1853. Essai sur l'inégalité des Races humaines. Didot, Paris.

González Burchard, E., Ziv, E., Coyle, N., et al., 2003. The importance of race and ethnic background in biomedical research and clinical practice. The New England Journal of Medicine 348, 1170–1175.

Goodman, A., 2003. http://www.pbs.org/race/000_About/002_04-background-01-07.htm.

Graves, J.L., 2014. Why This Book on Genetics and Race Is a Problem. https://evolution-institute.org/article/book-review-great-are-wades-errors-in-a-troublesome-inheritance-genes-race/.

Gravlee, C.C., 2009. How race becomes biology: embodiment of social inequality. American Journal of Physical Anthropology 139, 47–57.

Harpending, H., 2002. Race. Population genetics perspective. In: Pagel, M. (Ed.), Encyclopedia of Evolution, pp. 979–981.

Hartl, D.L., 1985. Our Uncertain Heritage: Genetics and Human Diversity, second ed. Harper & Row, New York.

Hellenthal, G., Busby, G.B.J., Band, G., et al., 2014. A genetic atlas of human admixture history. Science 343, 747–751.

Herrnstein, R.J., Murray, C., 1994. The Bell Curve: Intelligence and Class Structure in American Life. The Free Press.

Hey, J., 2001. The mind of the species problem. Trends in Ecology & Evolution 16, 326–329.

Hooton, E.A., 1926. Methods of racial analysis. Science 63, 75–81.

HoSang, D.M., 2014. On racial speculation and racial science: a response to Shiao et al. Sociological Theory 32 (228), 243.

Hunley, K.L., Healy, M.E., Long, J.C., 2009. The global pattern of gene identity variation reveals a history of long-range migrations, bottlenecks, and local mate exchange: implications for biological race. American Journal of Physical Anthropology 139, 35–46.

Huston, N., Raymond, M., 17 May 2013. Oui, les races existent. Le Monde.

Jacquard, A., 1982. Au péril de la science? Interrogations d'un généticien. Seuil, Paris.

Jordan, B., 2008. L'humanité au pluriel. La génétique et la question des races. Editions du Seuil, Paris.

Jorde, L.B., Wooding, S.P., 2004. Genetic variation, classification and "race". Nature Genetics 36, S28–S32.

Keita, S.O.Y., Kittles, R.A., Royal, C.D.M., et al., 2004. Conceptualizing human variation. Nature Genetics 36, S17–S20.

King, R.C., Stansfield, W.D., 1990. A Dictionnary of Genetics, fourth ed. Oxford University Press New York, Oxford.

Klarsfeld, A., Vernier, P., 1998. La biologie au service de l'antiracisme: limites et dangers. Médecine/Sciences 11, 1292–1294.

Kollewe, J., 17 February 2012. DNA machine can sequence human genomes in hours. The Guardian.

Kubota, J.T., Banaji, M.R., Phelps, E.A., 2012. The neuroscience of race. Nature Neuroscience 15, 940–948.

Le Petit Larousse Illustré, 2009. Larousse, Paris.

Lee, S.S., Mountain, J., Koenig, B., et al., 2008. The ethics of characterizing difference: guiding principles on using racial categories in human genetics. Genome Biology 9, 404. http://dx.doi.org/10.1186/gb-2008-9-7-404.

Lent, H., Wygodzinsky, P., 1979. Revision of the Triatominae (Hemiptera, Reduviidae), and their significance as vectors of Chagas disease. Bulletin of the American Museum of Natural History 163, 127–516.

Leroi, A.M., 2005. A Family Tree in Every Gene. The New York Times. March 14.

Leslie, S., Winney, B., Hellenthal, G., et al., 2015. The fine-scale genetic structure of the British population. Nature 519, 309–314.

Lewontin, R.C., 1972. The apportionment of human diversity. Evolutionary Biology 6, 381–398.

Lherminier, P., Solignac, M., 2005. De L'espèce. Editions Syllepse, Paris.

Lieberman, L., Hampton, R.E., Littlefield, A., Hallead, G., 1992. Race in biology and anthropology: a study of college texts and professors. Journal of Research in Science Teaching 29, 301–321.

Linnaeus, C., 1758. Systema naturae per regna tria naturae :secundum classes, ordines, genera, species, cum characteribus, differentiis, synonymis, locis (in Latin), tenth ed. Laurentius Salvius, Stockholm.

Livingstone, F., 1962. On the non-existence of human races. Current Anthropology 3, 279–281.

Long, J.C., Kittles, R.A., 2003. Human genetic diversity and the nonexistence of biological races. Human Biology 75, 449–471.

Long, J.C., Li, J., Healy, M.E., 2009. Human DNA sequences: more variation and less race. American Journal of Physical Anthropology 139, 23–34.

Longobardi, G., Ghirotto, S., Guardiano, C., et al., 2015. Across language families: genome diversity mirrors linguistic variation within Europe. American Journal of Physical Anthropology 157, 630–640.

Malik, K., 2012. Why Both Sides Are Wrong in the Race Debate. Pandaemonium. https://kenanmalik.wordpress.com/2012/03/04/why-both-sides-are-wrong-in-the-race-debate/.

Marks, J., 2014. The Genes Made Us Do it. The New Pseudoscience of Racial Difference. In These Times. http://www.inthesetimes.com.

Mayr, E., 2002. The biology of race and the concept of equality. Daedalus 131 (1), 89–94. On Inequality (Winter, 2002). http://www.gnxp.com/MT2/archives/001951.html.

Mersha, T.B., Abebe, T., 2015. Self-reported race/ethnicity in the age of genomic research: its potential impact on understanding health disparities. Human Genomics. http://dx.doi.org/10.1186/s40246-014-0023-x.

Miotto, O., Almagro-Garcia, J., Manske, M., et al., 2013. Multiple populations of artemisinin-resistant *Plasmodium falciparum* in Cambodia. Nature Genetics 45, 648–655.

Moreno-Estrada, A., Gignoux, C.R., Fernández-López, J.C., et al., 2014. The genetics of Mexico recapitulates Native American substructure and affects biomedical traits. Science 344, 1280–1285.

Morning, A., 2014. Does genomics challenge the social construction of race? Sociological Theory 32, 189–207.

Mountain, J.L., Risch, N., 2004. Assessing genetic contribution to phenotypic differences among "racial" and "ethnic" groups. Nature Genetics 36, S48–S53.

Need, A.C., Kasperavičiūtė, D., Cirulli, E.T., Goldstein, D.B., 2009. A genome-wide genetic signature of Jewish ancestry perfectly separates individuals with and without full Jewish ancestry in a large random sample of European Americans. Genome Biology 10, R7.

Nei, M., 1978. The theory of genetic distance and evolution of human races. Japanese Journal of Human Genetics 23, 341–369.

Ousley, S., Jantz, R., Freid, D., 2009. Understanding race and human variation: why forensic anthropologists are good at identifying race. American Journal of Physical Anthropology 139, 68–76.

Patrinos, A., 2004. Race and the human genome. Sponsor's forward. Nature Genetics 36, S1–S2.

PBS, 2003. Race: The Power of an Illusion. http://www.pbs.org/race/000_General/000_00-Home.htm.

Pigliucci, M., 2013. What are we to make of the concept of race? Thoughts of a philosopher–scientist. Studies in History and Philosophy of Biological and Biomedical Sciences 44, 272–277.

Reardon, J., 2005. Race to the Finish: Identity and Governance in an Age of Genomics. Princeton Univ. Press, Princeton, Oxford.

Relethford, J.H., 2009. Race and global patterns of phenotypic variation. American Journal of Physical Anthropology 139, 16–22.

Richardson, S.S., 2011. Race and IQ in the postgenomic age: the microcephaly case. BioSocieties 6, 420–446.

Risch, N., Burchard, E., Ziv, E., Tang, H., 2002. Categorization of humans in biomedical research: genes, race and disease. Genome Biology 3 (7) comment2007.1–2007.12.

Romualdi, C., Balding, D., Naside, I.S., et al., 2002. Patterns of human diversity, within and among continents, inferred from biallelic DNA polymorphisms. Genome Research 12, 602–612.

Rose, S., 2009. Should scientists study race and IQ? NO: science and society do not benefit. Nature 457, 786–788.

Rosenberg, N.A., Pritchard, J.K., Weber, J.L., et al., 2002. Genetic structure of human populations. Science 298, 2381–2385.

Rosenberg, N.A., Mahajan, S., Ramachandran, S., et al., 2005. Clines, clusters, and the effect of study design on the inference of human population structure. PLoS Genetics 1 (6), e70.

Rotimi, C.N., 2004. Are medical and nonmedical uses of large-scale genomic markers conflating genetics and "race"? Nature Genetics 36, S43–S47.

Rushton, J.P., Jensen, A.R., 2006. The totality of available evidence shows the race IQ gap still remains. Psychological Science 17, 921–922.

Sarich, V., Miele, F., 2004. Race: The Reality of Human Differences. Westview Press, Boulder, Colorado, USA.

Schwartz, R.S., 2001. Racial profiling in medical research. The New England Journal of Medicine 344, 1392–1393.

Shiao, J.L., Bode, T., Beyer, A., Selvig, D., 2012. The genomic challenge to the social construction of race. Sociological Theory 30, 67–88.

Sneath, P.H.A., Sokal, R.R., 1973. In: Kennedy, D., Park, R.B. (Eds.), Numerical Taxonomy. The Principle and Practice of Numerical Classification. Freeman, San Francisco, p. 537.

Sparks, C.S., Jantz, R.L., 2002. A reassessment of human cranial plasticity: boas revisited. Proceedings of the National Academy of Sciences of the United States of America 99, 14636–14639.

Taguieff, P.A., 1988. La Force du Préjugé. Essai sur le Racisme et ses Doubles. Armillaire la découverte Paris.

Tang, H., Quertermous, T., Rodriguez, B., et al., 2005. Genetic structure, self-identified race/ethnicity, and confounding in case-control association studies. The American Journal of Human Genetics 76, 268–275.

Tate, S.K., Goldstein, D.B., 2004. Will tomorrow's medicine work for everyone? Nature Genetics 36, S34–S42.

Templeton, A.R., 1999. Human races: a genetic and evolutionary perspective. American Anthropologist 100, 632–650.

Templeton, A.R., 2012. Gene flow, haplotype patterns and modern human origins. In: eLS. John Wiley & Sons, Ltd, Chichester. http://dx.doi.org/10.1002/9780470015902.a0020795.pub2.

Templeton, A.R., 2013. Biological races in humans. Studies in History and Philosophy of Biological and Biomedical Sciences 44, 262–271.

The 1000 Genomes Project Consortium, 2012. An integrated map of genetic variation from 1,092 human genomes. Nature 491, 56–65.

Tibayrenc, M., Ayala, F.J., 2012. Reproductive clonality of pathogens: a perspective on pathogenic viruses, bacteria, fungi, and parasitic protozoa. Proceedings of the National Academy of Sciences of the United States of America 109 (48), E3305–E3313.

Tibayrenc, M., Ayala, F.J., 2013. How clonal are *Trypanosoma* and *Leishmania?* Trends in Parasitology 29, 264–269.

Tibayrenc, M., 2006. The species concept in parasites and other pathogens: a pragmatic approach? Trends in Parasitology 22, 66–70.

Tishkoff, S.A., Kidd, K.K., 2004. Implications of biogeography of human populations for "race" and medicine. Nature Genetics 36, S21–S27.

Vallois, H.V., 1976. Les Races Humaines. Presses Universitaires de France, Paris.

Vincent, C., 16 December 2010. La fonte de la banquise donne naissance au "pizzly". Le Monde.

Vitti, J.J., Cho, M.K., Sarah, A., Tishkoff, S.A., Sabeti, P.C., 2012. Human evolutionary genomics: ethical and interpretive issues. Trends in Genetics 28, 137–145.

vonHoldt, B.M., Pollinger, J.P., Lohmueller, K.E., et al., 2010. Genome-wide SNP and haplotype analyses reveal a rich history underlying dog domestication. Nature 464, 898–902.

Wade, N., 2015. A Troublesome Inheritance. Genes, Race and Human History. Penguin books, New York.

Wolpoff, M.H., 2009. How Neandertals inform human variation. American Journal of Physical Anthropology 139, 91–102.

Woodley, M.A., Rindermann, H., Bell, E., et al., 2014. The relationship between microcephalin, ASPM and intelligence: a reconsideration. Intelligence 44, 51–63.

Woodley, M.A., 2010. Is *Homo sapiens* polytypic? Human taxonomic diversity and its implications. Medical Hypotheses 74, 195–201.

Yu, L., Li, Q.W., Ryder, O.A., Zhanga, Y.P., 2004. Phylogeny of the bears (Ursidae) based on nuclear and mitochondrial genes. Molecular Phylogenetics and Evolution 32, 480–494.

Yudell, M., Roberts, D., DeSalle, R., Tishkoff, S., 2016. Taking race out of human genetics. Science 351, 564–565.

Chapter 38

Social Darwinism

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In 1877, in a highly technical discussion of landholding in Ireland, Joseph Fisher wrote: "I can find nothing in the Brehon laws to warrant this theory of social Darwinism, and believe further study will show that the *Cain Saerrath* and the *Cain Aigillue* relate solely to what we now call chattels, and did not in any way affect what we now call the freehold, the possession of the land" (Fisher, 1877). Cain Saerrath refers to laws to do with honor and personal relationships and Cain Aigillue to laws to do with forfeits and fines, and Fisher is arguing that the holding of large tracts of land by individuals is not warranted by traditional law. Exactly why he spoke of "social Darwinism" is not made clear, although obviously he has Darwin's theory in mind, especially the thoughts about the struggle for existence. Even so, it is not at all clear that he thinks of social Darwinism as a unit, as a single identifiable concept, or rather as simply Darwinism in a social situation. Clearly, he is using the language of social Darwinism in a negative way, but as such there is no justification for the claim (nor is it being made) that social Darwinism is always something negative (Leonard, 2009).

Social Darwinism, however you read it, was not a term that took off rapidly. There are estimated to be no more than about a dozen usages of the term before the First World War, and this the time when historians usually argue that Social Darwinism was at its most vigorous. In fact, it was not until the Second World War that the term really became popular, thanks to the American historian Richard Hofstadter's use of the term in his *Social Darwinism in American Thought* (1944). It entered the discourse of scholars and remains prominently so to this day. Given this somewhat, shall we say, ambiguous history, it therefore behooves us to take care about the term's meaning and its proper application. Let us start our inquiry with Darwin himself.

CHARLES DARWIN

Darwin's theory of evolution through natural selection, as given in the *Origin of Species* (1859) is straightforward. First, there is the argument to the struggle for existence:

> *A struggle for existence inevitably follows from the high rate at which all organic beings tend to increase. Every being, which during its natural lifetime produces several eggs or seeds, must suffer destruction during some period of its life, and during some season or occasional year, otherwise, on the principle of geometrical increase, its numbers would quickly become so inordinately great that no country could support the product. Hence, as more individuals are produced than can possibly survive, there must in every case be a struggle for existence, either one individual with another of the same species, or with the individuals of distinct species, or with the physical conditions of life.*
>
> Darwin (1859, pp. 63–64)

Then, drawing on the fact that whenever you have a population of organisms, you find that there are differences between them and that every now and then something new seems to pop up into being, there is the argument to natural selection.

> *Let it be borne in mind how infinitely complex and close-fitting are the mutual relations of all organic beings to each other and to their physical conditions of life. Can it, then, be thought improbable, seeing that variations useful to man have undoubtedly occurred, that other variations useful in some way to each being in the great and complex battle of life, should sometimes occur in the course of thousands of generations? If such do occur, can we doubt (remembering that many more individuals are born than can possibly survive) that individuals having any advantage, however slight, over others, would have the best chance of surviving and of procreating their kind? On the other hand, we may feel sure that any variation in the least degree injurious would be rigidly destroyed. This preservation of favourable variations and the rejection of injurious variations, I call Natural Selection.*
>
> Darwin (1859, pp. 80–81)

Do note that, for Darwin, change is not random. Certain features lead to success. Others do not. This means that the successful features have virtues not possessed by the

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00038-7

unsuccessful; features like the hand and the eye are "as if" designed for their ends—they are "adaptations."

So much for the "Darwinism" part of the equation. Now for the "social." In the *Origin of Species* Darwin said very little about our species. He had always believed fully that his theory applied to humankind, but before the controversy started, he had wanted first to get the main ideas on the table. Twelve years later, in the *Descent of Man* (1871), he grasped the nettle and took up human evolution, both physical and sociocultural. There was some social discussion in the *Descent*—in this respect it was different from the *Origin*—although much of it was not about European societies and was instead more about what Darwin and his fellows would have called "savages." (This was apart from the fact that much of the *Descent* was not about human beings at all, but about sexual selection in the animal world. Darwin was preparing the way to argue that sexual selection had been crucial in human evolution, especially in making for racial differences.)

Darwin first had to argue that natural selection could lead to a social situation at all. It was not the case that, from a biological perspective, the struggle just led to outright hostility, competition, and warfare, and that anything social must be imposed from without, almost by force. Darwin had faced this problem in the *Origin* when dealing with the social insects. His solution there to the problem of "altruism" (as it was called) was to suggest that it comes about because of relatedness. Organisms show help to others if they are related. Although Darwin did not have the language of genetics, he would have agreed with today's thinkers who argue that inasmuch as relatives reproduce, one is oneself reproducing by proxy because you share units of heredity (genes) with relatives (Hamilton, 1964).

In the *Descent*, Darwin broadened this discussion out a little. He agreed that sociality could come about through nonrelatives via what today is known as "reciprocal altruism"—ie, you scratch my back and I will scratch yours (Trivers, 1971): "In the first place, as the reasoning powers and foresight of the members became improved, each man would soon learn that if he aided his fellow-men, he would commonly receive aid in return. From this low motive he might acquire the habit of aiding his fellows; and the habit of performing benevolent actions certainly strengthens the feeling of sympathy which gives the first impulse to benevolent actions. Habits, moreover, followed during many generations probably tend to be inherited" (Darwin, 1871, pp. 1, 163–164). Then Darwin added: "But there is another and much more powerful stimulus to the development of the social virtues, namely, the praise and the blame of our fellow-men. The love of approbation and the dread of infamy, as well as the bestowal of praise of blame, are primarily due, as we have seen in the third chapter, to the instinct of sympathy; and this instinct no doubt was originally acquired, like all the other social instincts, through natural selection" (pp. 1, 164). He elaborated: "To do good unto others—to do unto others as ye would they should do unto you—is the foundation-stone of morality. It is, therefore, hardly possible to exaggerate the importance during rude times of the love of praise and the dread of blame" (pp. 1, 165).

Darwin then went into detail: "It must not be forgotten that although a high standard of morality gives but a slight or no advantage to each individual man and his children over the other men of the same tribe, yet that an advancement in the standard of morality and an increase in the number of well-endowed men will certainly give an immense advantage to one tribe over another" (pp. 1, 166). Darwin doesn't mince words about what this means: "There can be no doubt that a tribe including many members who, from possessing in a high degree the spirit of patriotism, fidelity, obedience, courage, and sympathy, were always ready to give aid to each other and to sacrifice themselves for the common good, would be victorious over most other tribes; and this would be natural selection." And so we get the consequence. "At all times throughout the world tribes have supplanted other tribes; and as morality is one element in their success, the standard of morality and the number of well-endowed men will thus everywhere tend to rise and increase." Darwin was not now breaking from the thinking of the *Origin*. He made it clear that he regarded tribes as interrelated families, and the family he took to be one individual, a kind of superorganism. In other words, with respect to morality, just as with the ants, humans are parts of a whole rather than individuals in their own right (Richards and Ruse, 2016).

SOCIAL VIEWS

Laid on top of this we get the views of an upper-middle-class Englishman whose family money came from trade. On the one hand, like almost everyone else on mainland Britain, Darwin feared and despised the Irish, worrying about their unrestrained family sizes:[1]

> *[T]he reckless, degraded, and often vicious members of society, tend to increase at a quicker rate than the provident and generally virtuous members. Or as Mr. Greg puts the case: 'The careless, squalid, unaspiring Irishman multiplies like rabbits: the frugal, foreseeing, self-respecting, ambitious Scot, stern in his morality, spiritual in his faith, sagacious and disciplined in his intelligence, passes his best years in struggle and in celibacy, marries late, and leaves few behind him. Given a land originally peopled by a thousand Saxons and a thousand Celts—and in a dozen*

1. Comparatively, the Irish were a much bigger issue in the 19th century, with about 5 million inhabitants compared to 10 million on mainland Great Britain (England, Wales, and Scotland). Today there are about 5 million people compared to over 60 million in Great Britain. Whoever was to blame, the fact is that the Irish were poor and, when in Great Britain, rarely seen to great advantage, crammed into the slums of big cities, such as Liverpool.

generations five-sixths of the population would be Celts, but five-sixths of the property, of the power, of the intellect, would belong to the one-sixth of Saxons that remained. In the eternal 'struggle for existence,' it would be the inferior and less *favoured race that had prevailed—and prevailed by virtue not of its good qualities but of its faults.'*

Darwin (1871, pp. 1, 174)

Fortunately there are some balancing factors, mainly that the children of poor, unthinking people die off more quickly than the children of wise and sensible people. It is not a matter of who is first out of the gate but of who crosses the finishing line first, and the Scots have it on the Irish in this respect. Not as much as the English of course, but then who does?!

One good thing about English society as far as Darwin was concerned was the firm commitment to capitalism. Interestingly, note here (for future reference) that it is not a question of who fails in the struggle but more of who wins:

In all civilised countries man accumulates property and bequeaths it to his children. So that the children in the same country do not by any means start fair in the race for success. But this is far from an unmixed evil; for without the accumulation of capital the arts could not progress; and it is chiefly through their power that the civilised races have extended, and are now everywhere extending, their range, so as to take the place of the lower races. Nor does the moderate accumulation of wealth interfere with the process of selection. When a poor man becomes rich, his children enter trades or professions in which there is struggle enough, so that the able in body and mind succeed best. The presence of a body of well-instructed men, who have not to labour for their daily bread, is important to a degree which cannot be over-estimated; as all high intellectual work is carried on by them, and on such work material progress of all kinds mainly depends, not to mention other and higher advantages. No doubt wealth when very great tends to convert men into useless drones, but their number is never large; and some degree of elimination here occurs, as we daily see rich men, who happen to be fools or profligate, squandering away all their wealth.

Darwin (1871, vol. 1, pp. 169–170)

Darwin, the child of capitalism—actually the grandchild of capitalism because it was his mother's father Josiah Wedgwood who made the family money with his pottery works—had little time for primogeniture. This was the practice of aristocrats passing on their land and possessions to their oldest sons. As far as Darwin was concerned, all children (certainly all boys) deserved an equal cut. As expectedly, Darwin had little time for unions. Writing to a German correspondent in 1872, Darwin said: "I much wish that you would sometimes take occasion to discuss an allied point, if it holds good on the continent,—namely the rule insisted on by all our Trades-Unions, that all workmen,—the good and bad, the strong and weak,—sh[oul]d all work for the same number of hours and receive the same wages." Adding: "I fear that Cooperative Societies, which many look at as the main hope for the future, likewise exclude competition. This seems to me a great evil for the future progress of mankind" (Darwin, 1985, pp. 20, 324).[2]

We can see, therefore, that historically we can make a claim for Charles Darwin being a social Darwinian, whatever language one uses. One senses, however, that the sociopolitical consequences he drew from his theory were less to do with the mechanics of the theory—even the struggle for existence—and more with the inherited beliefs that he held. Someone with different beliefs might go another way. And indeed this was so. The co-discoverer of natural selection, Alfred Russel Wallace, was a socialist—he had heard the Scottish industrialist and socialist Robert Owen when he was an impressionable teenager—and he always thought that natural selection pointed that way (Wallace, 1905). Unlike Darwin who always thought that natural selection favors the individual—and that hence altruism and other social sentiments had to be explained in terms of benefit to the individual—Wallace thought that natural selection can favor the group, up to and including the species (Ruse, 1980). For him, it came naturally to argue that within the human species we have sentiments promoting group harmony, which he translated as socialism.

More extreme was Prince Peter Kropotkin, who argued that there is an evolved sentiment of mutual aid and that

2. A topic often linked to social Darwinism is that of eugenics, the idea of selective breeding of humans to improve them. This was a theme started and promoted by Darwin's cousin Francis Galton. Generally, those most into social Darwinism were more interested in society as it is or can be changed through social means, rather than plans for biological change. Darwin himself drew back somewhat from eugenics. He recognized the problem (referencing Galton as his source of information):

With savages, the weak in body or mind are soon eliminated; and those that survive commonly exhibit a vigorous state of health. We civilised men, on the other hand, do our utmost to check the process of elimination; we build asylums for the imbecile, the maimed, and the sick; we institute poor-laws; and our medical men exert their utmost skill to save the life of every one to the last moment. There is reason to believe that vaccination has preserved thousands, who from a weak constitution would formerly have succumbed to small-pox. Thus the weak members of civilised societies propagate their kind. No one who has attended to the breeding of domestic animals will doubt that this must be highly injurious to the race of man. It is surprising how soon a want of care, or care wrongly directed, leads to the degeneration of a domestic race; but excepting in the case of man himself, hardly any one is so ignorant as to allow his worst animals to breed (Darwin, 1871, vol. 1, p. 168). That said, Darwin pulled back from offering any solution. We feel sympathy for life's unfortunates, and so be it: "Nor could we check our sympathy, if so urged by hard reason, without deterioration in the noblest part of our nature."

this leads to harmonious interactions of such intensity that we should abolish the state entirely and adopt an anarchist philosophy of life.

> *[W]henever mankind had to work out a new social organization, adapted to a new phase of development, its constructive genius always drew the elements and the inspiration for the new departure from that same ever-living tendency. New economical and social institutions, in so far as they were a creation of the masses, new ethical systems, and new religions, all have originated from the same source, and the ethical progress of our race, viewed in its broad lines, appears as a gradual extension of the mutual-aid principles from the tribe to always larger and larger agglomerations, so as to finally embrace one day the whole of mankind, without respect to its divers creeds, languages, and races.*
>
> Kropotkin (1902)

HERBERT SPENCER

Pause for a moment and ask why Darwin would have thought that capitalism was a good thing. No so much why it happens, but why it is good that it happens. Clearly in some sense because he believed in societal progress. He thought that a capitalist society would function better than other societies and that this would lead to improvement. Similar sorts of thinking obviously lay behind his views on the Irish. If they just outbreed the Scots, then we are facing degeneration, and that is not a good thing. We do know in fact that although Darwin denied that there was a built-in principle of progress within his theory, he did believe that his theory led to biological progress and that ultimately human progress would be part and parcel of this. He thought that there would be what modern-day biologists call "arms races" between lines of evolving organisms, and that this would lead to improvement. In the third edition of the *Origin* (1861) he wrote as follows:

> *If we look at the differentiation and specialisation of the several organs of each being when adult (and this will include the advancement of the brain for intellectual purposes) as the best standard of highness of organisation, natural selection clearly leads towards highness; for all physiologists admit that the specialisation of organs, inasmuch as they perform in this state their functions better, is an advantage to each being; and hence the accumulation of variations tending towards specialisation is within the scope of natural selection.*
>
> Darwin (1861, p. 134)

Talk of such progress brings us around to the other key figure in any discussion of Social Darwinism, Darwin's fellow English evolutionist Herbert Spencer. In fact, far more than Darwin, it is Spencer's name that comes first to mind in any discussion of social Darwinism, for he is thought to be the epitome of any and all calls for society to be built on the foundation of natural selection, brought on by the struggle for existence. However, while there is obvious truth in this, we do need to tread carefully. First, there is no doubt that Spencer did articulate sentiments that seem to be pure social Darwinism (as it is generally understood). He is well known for his tough stand on social issues, and these—commonly known as *laissez faire*—seem to be a straight transfer from biology and the Darwinian process of struggle and selection.

> *We must call those spurious philanthropists, who, to prevent present misery, would entail greater misery upon future generations. All defenders of a Poor Law must, however, be classed among such. That rigorous necessity which, when allowed to act on them, becomes so sharp a spur to the lazy and so strong a bridle to the random, these pauper's friends would repeal, because of the wailing it here and there produces. Blind to the fact that under the natural order of things, society is constantly excreting its unhealthy, imbecile, slow, vacillating, faithless members, these unthinking, though well-meaning, men advocate an interference which not only stops the purifying process but even increases the vitiation—absolutely encourages the multiplication of the reckless and incompetent by offering them an unfailing provision, and* discourages *the multiplication of the competent and provident by heightening the prospective difficulty of maintaining a family.*
>
> Spencer (1851, pp. 323–324)

This sounds like Margaret Thatcher at her most militant, and the analogy is not misplaced. Both Spencer and Thatcher came from the lower-middle classes, in the British Midlands, raised in nonconformist (dissenters') families. This means they were outside the upper echelons of society (unlike Darwin) and there was an element of resentment—a feeling that the state benefits those in power or those that are totally unworthy and that the hard working and illustrious (themselves) did not get the respect that they deserved.[3]

3. In this context, Spencer sounds a bit like Darwin with respect to the degeneration of the race because of society's unfortunates:

> *Besides an habitual neglect of the fact that the quality of a society is physically lowered by the artificial preservation of its feeblest members, there is an habitual neglect of the fact that the quality of a society is lowered morally and intellectually, by the artificial preservation of those who are least able to take care of themselves… For if the unworthy are helped to increase, by shielding them from that mortality which their unworthiness would naturally entail, the effect is to produce, generation after generation, a greater unworthiness.*
>
> Richards (1987, p. 303).

Second, above all others, it was Spencer who pushed the notion of progress. Indeed, he saw organic evolution as being but one facet of the overall upward progress that characterizes the whole world process: from the undifferentiated to the differentiated, or in his words from the homogeneous to the heterogeneous:

> *Now we propose in the first place to show, that this law of organic progress is the law of all progress. Whether it be in the development of the Earth, in the development of Life upon its surface, in the development of Society, of Government, of Manufactures, of Commerce, of Language, Literature, Science, Art, this same evolution of the simple into the complex, through successive differentiations, hold throughout. From the earliest traceable cosmical changes down to the latest results of civilization, we shall find that the transformation of the homogeneous into the heterogeneous, is that in which Progress essentially consists.*
>
> Spencer (1857, pp. 2–3)

Nothing escapes this law. Humans are more complex or heterogeneous than other animals; Europeans are more complex or heterogeneous than savages; and (hardly a surprise) the English language is more complex or heterogeneous than the languages of other speakers. Spencer combined all of this with his views on the basis of ethics, arguing that morality emerges through the evolutionary process and our duties are to ensure that this happens by removing barriers and facilitating the process. "Ethics has for its subject-matter, that form which universal conduct assumes during the last stages of its evolution" (Spencer, 1879, p. 21). Continuing: "And there has followed the corollary that conduct gains ethical sanction in proportion as the activities, becoming less and less militant and more and more industrial, are such as do not necessitate mutual injury or hindrance, but consist with, and are furthered by, co-operation and mutual aid."

Third, a lot of people (especially in America) picked up on this. Given the rough and tough society in which they lived, they found that the Spencerian philosophy spoke to them. Leading barons of industry like Andrew Carnegie, the great steel magnate, and John D. Rockefeller, of Standard Oil fame, were enthusiasts—"The law of competition may be sometimes hard for the individual, [but] it is best for the race, because it insures the survival of the fittest in every department" (Andrew Carnegie, 1889)—as were some of the professors and others who wrote on these things: "A drunkard in the gutter is just where he ought to be…The law of survival of the fittest was not made by man, and it cannot be abrogated by man. We can only, by interfering with it, produce the survival of the unfittest" (Sumner, 1914).

Or think of some of the fiction:

> *His teeth closed on Spitz's left fore leg. There was a crunch of breaking bone, and the white dog faced him on three legs. Thrice he tried to knock him over, then repeated the trick and broke the right fore leg. Despite the pain and helplessness, Spitz struggled madly to keep up. He saw the silent circle, with gleaming eyes, lolling tongues, and silvery breaths drifting upward, closing in upon him as he had seen similar circles close in upon beaten antagonists in the past. Only this time he was the one who was beaten.*
>
> *There was no hope for him. Buck was inexorable. Mercy was a thing reserved for gentler climes. (London, 1903, p. 24)*

This is from *The Call of the Wild*, by Spencer-enthusiast Jack London.

POINTS TO CONSIDER

And yet, the story is never quite this simple. Consider the following five points that complexify the situation. First, although Spencer did indeed discover natural selection independently of Darwin and always endorsed it somewhat, it was never his primary mechanism of change. He was always first and foremost a Lamarckian, thinking that real change comes about through the inheritance of acquired characteristics. The struggle for Spencer was a spur to action that would make for new features that could then be passed along directly. Although he certainly did think that some lost, in a funny way Spencerian evolution would keep going if there were no losers, so long as everyone kept striving to succeed (Spencer, 1852).

Second, connected with this point at least in part was the fact that Spencer was an organicist, thinking that society is like an organism and thus integrated with parts functioning together. Yes, there was struggle within the society, but the struggle was not to break it apart but rather to improve it.

> *The parts of an animal form a concrete whole, but the parts of society form a whole which is discrete. While the living units composing the one are bound together in close contact, the living unit composing the other are free, are not in contact, and are more or less widely dispersed… Though coherence among its parts is a prerequisite to that cooperation by which the life of an individual organism is carried on, and though the members of a social organism, not forming a concrete whole, cannot maintain cooperation by means of physical influences directly propagated from part to part, yet they can and do maintain cooperation by another agency. Not in contact, they nevertheless affect one another through intervening spaces, both by emotional language and by the language, oral and written of the*

> *intellect… That is to say, the internuncial function, not achievable by stimuli physically transferred, is nevertheless achieved by language.*
>
> Spencer (1860)

Third, Spencer was far from militant or harsh about everything. For instance—no doubt in part reflecting Quaker elements in his family—he was always against militancy, thinking that (real) arms races were a waste of time and money (Spencer, 1904). Especially deplorable was the arms race at the end of the 19th century between the British and German navies. He was also in favor of free trade, thinking that among other things this would encourage relationships between nations, if only from self-interest. His followers also were more nuanced than suggested. Like Darwin, they were more interested in the survival of the successful (which is what they tended to belong to) than the nonsurvival of the nonsuccessful. Consider for a moment the nature of Andrew Carnegie's great philanthropy. It was to found and support public libraries. These would be places where the poor but talented could go and improve themselves. All very Spencerian.

(Prince Peter Kropotkin, the anarchist, was another who pushed the idea of help, or what he called "mutual aid." See Kropotkin (1955), first published in 1903.)

Fourth, Spencer's long-time friend Thomas Henry Huxley—Darwin's great supporter and the grandfather of the novelist Aldous Huxley—finally got very irritated with claims that the evolutionary process leads progressively to better things and that therefore morality must be a function of trying to aid the evolutionary process. Indeed, in Huxley's opinion, it is often the case that those attributes that lead to success in the struggle are precisely those that we do not think well. "Man, the animal, in fact, has worked his way to the headship of the sentient world, and has become the superb animal which he is, in virtue of his success in the struggle for existence" (Huxley, 1893, p. 51). Continuing:

> *For his successful progress, throughout the savage state, man has been largely indebted to those qualities which he shares with the ape and the tiger; his exceptional physical organization; his cunning, his sociability, his curiosity, and his imitativeness; his ruthless and ferocious destructiveness when his anger is roused by opposition.*
>
> *But, in proportion as men have passed from anarchy to social organization, and in proportion as civilization has grown in worth, these deeply ingrained serviceable qualities have become defects. After the manner of successful persons, civilized man would gladly kick down the ladder by which he has climbed. He would be only too pleased to see "the ape and tiger die."*

(I discuss Huxley's essay in some detail in my edition of the essay, Ruse 2009.)

Fifth and finally, many people including those predisposed to Spencerian thinking saw the justice in Huxley's critique and modified their thinking accordingly. Jack London was one. On the one hand, he continued to see the virtues of Spencer's thinking and of how this would lead to better and more harmonious functioning. "Only Spitz quivered and bristled as he staggered back and forth, snarling with horrible menace, as though to frighten off impending death. Then Buck sprang in and out; but while he was in, shoulder had at last squarely met shoulder. The dark circle became a dot on the moon-flooded snow as Spitz disappeared from view. Buck stood and looked on, the successful champion, the dominant primordial beast who had made his kill and found it good" (London, 1903, p. 24). But it is more than just this. Everyone now benefits from Buck's success, dogs and men. "Highly as the dog-driver had forevalued Buck, with his two devils, he found, while the day was yet young, that he had undervalued. At a bound Buck took up the duties of leadership; and where judgment was required, and quick thinking and quick acting, he showed himself the superior even of Spitz, of whom Francois had never seen an equal" (p. 26).

On the other hand, London wrote tales that were far more in line with Huxley than with Spencer. In *The Scarlet Plague* (1912), a new disease wipes out almost all human beings. One of the survivors, a professor of classics, ruminates on the appalling behavior of people under such huge stresses, not to mention the often grotesque actions of those that do survive. One of the most successful was "an iniquitous, moral monster, a blot on the face of nature, a cruel, relentless, bestial cheat as well." The professor concludes in a very non-Spencerian fashion that Progress is never permanent and that the best we can do is fight the beast within us:

> *The gunpowder will come. Nothing can stop it—the same old story over and over. Man will increase, and men will fight. The gunpowder will enable men to kill millions of men, and in this way only, by fire and blood, will a new civilization, in some remote day, be evolved. And of what profit will it be? Just as the old civilization passed, so will the new. It may take fifty thousand years to build, but it will pass. All things pass.*

ADOLF HITLER

Let's move now fully into the 20th century. Whoever was responsible, we do find stark statements of a social Darwinian nature. Some of the more notorious were made by military men before and during the First World War. General Friedrich von Bernhardi, pushed out of the German army because he was signaling a little too bluntly the General Staff's intentions, left no place for the imagination in his best-selling *Germany and the Next War* (1912): "War

is a biological necessity," and hence, "Those forms survive which are able to procure themselves the most favourable conditions of life, and to assert themselves in the universal economy of nature. The weaker succumb." Progress depends on war: "Without war, inferior or decaying races would easily choke the growth of healthy budding elements, and a universal decadence would follow." And, anticipating horrible philosophies of the 20th century: "Might gives the right to occupy or to conquer. Might is at once the supreme right, and the dispute as to what is right is decided by the arbitrament of war. War gives a biologically just decision, since its decision rests on the very nature of things" (Bernhardi, 1912, p. 10, quoted by Crook, 1994, p. 83).

There is continuing debate about the extent to which Hitler can truly be labeled a social Darwinian. It is a popular cry by those who would discredit evolutionary thinking generally. "Darwin-led-to-Hitler-led-to-the-Holocaust" sort of thinking. Whether such guilt by association is fully merited is another matter. Lifted out of context, the story looks dire:

> *All great cultures of the past perished only because the originally creative race died out from blood poisoning.*
>
> *The ultimate cause of such a decline was their forgetting that all culture depends on men and not conversely; hence that to preserve a certain culture the man who creates it must be preserved. This preservation is bound up with the rigid law of necessity and the right to victory of the best and stronger in this world.*
>
> *Those who want to live, let them fight, and those who do not want to fight in this world of eternal struggle do not deserve to live.*
>
> Hitler (1925, p. 1, Chapter 11)

However, as always, things are a bit more complex than that. If you look at the supposedly Darwinian passages in context, you see that Hitler's real obsession is with racial purity, and this was certainly not Darwin's concern. Having said this, something had to lead to Hitler and obviously the 19th century bears much of the guilt. If you feel a slight sense of unease, I would not say that you are without justification, remembering, of course, that Darwin himself was not the only (some might say, not the chief) foundation for social Darwinism (Richards, 2008 discusses these issues in detail).

JULIAN HUXLEY

Moving toward the present, although the term social Darwinism is rarely used because of the negative connotations (although for some critics this is the very reason for using it), we do find that the kind of thinking that it represented persisted and indeed persists to the present day. Julian Huxley (the grandson of Thomas Henry Huxley and the older brother of the novelist Aldous Huxley) is a good case in point. He argued that evolution justifies an obsession with technology, science, and major public works. While Huxley was not uninterested in life at the personal level, it was the general domain which really excited him.

> *All claims that the State has an intrinsically higher value than the individual are false. They turn out, on closer scrutiny, to be rationalizations or myths aimed at securing greater power or privilege for a limited group which controls the machinery of the State. On the other hand the individual is meaningless in isolation, and the possibilities of development and self-realization open to him are conditioned and limited by the nature of the social organization. The individual thus has duties and responsibilities as well as rights and privileges, or if you prefer it, finds certain outlets and satisfactions (such as devotion to a cause, or participation in a joint enterprise) only in relation to the type of society in which he lives.*
>
> Huxley (1934, pp. 138–139)

The key moral principle seems to have been for the need of planning in running the state and, above all, the application of scientific principles and results in such planning and its implementation. You simply cannot (or should not) leave things to chance or intuition—the implication being that this is precisely where your average politician does leave things—but should bring the trained scientific mind to bear on life's problems.

Again and again Huxley returned to this theme. For instance, in a book which he wrote in the interwar years, *If I Were Dictator* (1934), he stressed the need for science in the running of an efficient state and that such science would need to be of the social variety as well as physicochemical and biological. During the Second World War, he wrote a highly laudatory essay on the Tennessee Valley Authority, that marvel of the Rooseveltian New Deal, whereby the federal government built and ran a massive system of river damming and irrigation in what had hitherto been one of the more desolate parts of the United States (Huxley, 1943). Then, after the War it was Huxley who insisted on science being added to UNESCO, and he wrote a vigorous polemic arguing that the organization had to be run on evolutionary lines—lines demanding lots of science. So vigorous was his polemic indeed that he upset his masters and he was refused a full four-year term as director general.[4]

4. Huxley was interested in eugenics, but obviously for him as for most the appalling things done by the National Socialists damped much enthusiasm. It is probably fair to say that (again like most) Huxley moved from an earlier hope that genetics might be used actually to produce better quality humans to a more limited belief and hope that genetics might be used to prevent horrendous pains and illnesses—genetic counseling of the kind, for instance, that is often offered to Ashkenazi Jews who fear they might be the carriers of genes for Tay-Sachs disease.

What is interesting, and perhaps to be expected in the light of our discussion, is that Huxley was a fanatic about evolutionary progress, thinking that it justifies moral behavior. Our ethical duty is to work with and within this process to see that it is realized as fully as possible.

> *The teleologically-minded would say that this trend [progress] embodies evolution's purpose. I do not feel that we should use the word purpose save where we know that a conscious aim is involved; but we can say that this is the* most desirable *direction of evolution, and accordingly that our ethical standards must fit into its dynamic framework. In other words, it is ethically right to aim at whatever will promote the increasingly full realization of increasingly higher values.*
>
> Huxley (1943, p. 42)

Similar Sentiments Come out in his Polemic for UNESCO:

> *From the evolutionary point of view, the destiny of man may be summed up very simply: it is to realize the maximum progress in the minimum time. That is why the philosophy of Unesco must have an evolutionary background, and why the concept of progress cannot but occupy a central position in that philosophy.*
>
> Huxley (1948, p. 11)

EDWARD O. WILSON

More recently it is the Harvard evolutionist—ant specialist and sociobiologist—Edward O. Wilson who has been pushing moral action in the name of evolution. He sees all of life as an interconnected whole. This is expressed through his "biophilia" hypothesis: "To explore and affiliate with life is a deep and complicated process in mental development. To an extent still undervalued in philosophy and religion, our existence depends on this propensity, our spirit is woven from it, hope rises on its currents" (1984). Individual organisms, individual species, are part of a larger network and no one or group can take itself apart in isolation. Morally, therefore, our obligation is to preserve (human) life. Explicitly, Wilson sees the significance of sustainability and of the cherishing of the environment and the preservation of species in terms of human welfare. If we destroy the rainforests of South America in pursuit of short-term ends like cattle rearing, we stand in danger of destroying many plants that could in the future prove to have invaluable medicinal properties.

We must therefore tackle the paradox of "the two themes that form the fundamental basis of ethics, the expanding-circle theme that gives rights to all species, versus the anthropocentric theme that measures all good in the coin of human welfare." This will be difficult but it will not be impossible. "The two are resolved in part by noting that for human survival and mental health and fulfillment we need the natural setting in which the human mind almost certainly evolved and in which culture has developed over these millions of years of evolution. Perhaps both of those arguments can be joined to create the prudence concerning the environment and our own populations that is so desperately needed."

Behind all of this lie very Spencerian themes: "the overall average across the history of life has moved from the simple and few to the more complex and numerous. During the past billion years, animals as a whole evolved upward in body size, feeding and defensive techniques, brain and behavioral complexity, social organization, and precision of environmental control—in each case farther from the nonliving state than their simpler antecedents did" (Wilson, 1992, p. 187). Wilson concludes: "Progress, then, is a property of the evolution of life as a whole by almost any conceivable intuitive standard, including the acquisition of goals and intentions in the behavior of animals."

CONCLUSION

We can bring our discussion to an end. For all that there are legitimate questions about the use of the term social Darwinism, it is clear that evolutionists, including Charles Darwin, have been interested in the social implications of evolutionary thinking. There have been differences about the basic biological theory, especially between the two with greatest call to be called the founders: Charles Darwin and Alfred Russel Wallace. Analogously, Charles Darwin and Herbert Spencer had profoundly different visions of the evolutionary process. There have also been differences about how the biology plays out in society—the differences, for instance, between Darwin and Wallace. There have been enthusiasts for social Darwinism—Spencer obviously—and there have been critics—Thomas Henry Huxley as obviously.

Social Darwinism, especially since the popularization of the term by Hofstadter, has generally been thought to be a problematic, if not outright wrong, philosophy of society. We have seen evidence that in the hands of some this is clearly true. I doubt there are many today who would stand up for the thinking of General von Bernhardi. On the other hand, it is by no means obvious that historically it has always been a philosophy that all decent people would reject. In many respects, Andrew Carnegie was not a particularly nice man. He could be brutal with his workers. The Homestead Strike in Pittsburgh is an example that will never—and should never—die. But he genuinely did believe what he said when he claimed that no man should die rich, and his founding of public libraries enriched the

lives of many—including this author, who grew up in a town in England with a Carnegie Library.

It is far from obvious that social Darwinism was responsible for all of the ills of which it stands accused. Something had to cause Hitler and the National Socialists, but even if evolutionary ideas played some role it was limited and there were other far bigger factors—the German Volkish movement from the 19th century and residual anti-Semitism to mention two factors. (And if a third is needed, the dislike of Hitter and the Nazi leaders for evolutionary ideas generally, which linked Arians with Jews.) Finally, forms of social Darwinism persist to this day, even though the term is rarely, if ever, used. At the social level, Julian Huxley and Edward O. Wilson have been among the most important evolutionists of the 20th century (and in Wilson's case, the 21st century). Let us leave it at that. If nothing else, we should have persuaded the reader that social Darwinism is something that still merits vigorous historical examination.

REFERENCES

Bernhardi, F.V., 1912. Germany and the Next War. Cotta, Stuttgart and Berlin.

Carnegie, A., 1889, 1962. The gospel of wealth. In: Kirkland, E.C. (Ed.), The Gospel of Wealth and Other Timely Essays. Harvard University Press, Cambridge, Mass, pp. 14–49.

Crook, P., 1994. Darwinism: War and History. University of Cambridge Press, Cambridge.

Darwin, C., 1859. On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life. John Murray, London.

Darwin, C., 1861. Origin of Species, third ed. John Murray, London.

Darwin, C., 1871. The Descent of Man, and Selection in Relation to Sex. John Murray, London.

Darwin, C., 1985. The Correspondence of Charles Darwin. Cambridge University Press, Cambridge.

Fisher, J., 1877. A history of landholding in Ireland. Transactions of the Royal Historical Society 5, 228–326, 424.

Hamilton, W.D., 1964. The genetical evolution of social behaviour. Journal of Theoretical Biology 7, 1–52.

Hitler, A., 1925. Mein Kampf. Secker and Warburg, London.

Hofstadter, R., 1944. Social Darwinism in American Thought. Beacon Press, Boston.

Huxley, T.H., 1893. Collected Essays: Darwiniana. Macmillan, London.

Huxley, J.S., 1934. If I Were Dictator. Harper and Brothers, New York and London.

Huxley, J.S., 1943. TVA: Adventure in Planning. Scientific Book Club, London.

Huxley, J.S., 1948. UNESCO: Its Purpose and Its Philosophy. Public Affairs Press, Washington, D.C.

Huxley, T.H., 2009. In: Ruse, M. (Ed.), Evolution and Ethics with a New Introduction. Princeton University Press, Princeton.

Kropotkin, P., 1902. Mutual Aid: A Factor in Evolution. Extending Horizons Books, Boston.

Kropotkin, P., 1955. Mutual Aid. Extending Horizons Books, Boston.

Leonard, T.C., 2009. Origins of the myth of social Darwinism: the ambiguous legacy of richard Hofstadter's social Darwinism in American thought. Journal of Economic Behavior and Organization 71, 37–51.

London, J., 1903. The Call of the Wild. Macmillan, New York.

London, J., 1912. The Scarlet Plague. London Magazine. Macmillan, New York.

Richards, R.J., 1987. Darwin and the Emergence of Evolutionary Theories of Mind and Behavior. University of Chicago Press, Chicago.

Richards, R.J., 2008. The Tragic Sense of Life: Ernst Haeckel and the Struggle over Evolutionary Thought. University of Chicago Press, Chicago.

Richards, R.J., Ruse, M., 2016. Debating Darwin. University of Chicago Press, Chicago.

Ruse, M., 1980. Charles Darwin and group selection. Annals of Science 37, 615–630.

Spencer, H., 1851. Social Statics; or the Conditions Essential to Human Happiness Specified and the First of Them Developed. J. Chapman, London.

Spencer, H., 1852. A theory of population, deduced from the general law of animal fertility. Westminster Review 1, 468–501.

Spencer, H., 1857. Progress: its law and cause. Westminster Review LXVII, 244–267.

Spencer, H., 1860. The social organism. Westminster Review 73, 90–121.

Spencer, H., 1879. The Data of Ethics. Williams and Norgate, London.

Spencer, H., 1904. Autobiography. Williams and Norgate, London.

Sumner, W.G., 1914. The Challenge of Facts and Other Essays. Yale University Press, New Haven.

Trivers, R.L., 1971. The evolution of reciprocal altruism. Quarterly Review of Biology 46, 35–57.

Wallace, A.R., 1905. My Life: A Record of Events and Opinions. Chapman and Hall, London.

Wilson, E.O., 1984. Biophilia. Harvard University Press, Cambridge, Mass.

Wilson, E.O., 1992. The Diversity of Life. Harvard University Press, Cambridge, Mass.

Chapter 39

History and Diversity of Religion

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RELIGIOUS VERSUS NONRELIGIOUS

In March 2014, I was in a cab in Bangkok, traveling to meet a monk at Wat Bowonniwet, a royal temple and the home of the late *sangha-rāja*, the head of the monastic community. For the previous 6 months, Bangkok had been wracked by protests about the political system, which would eventually lead to a military takeover in late May. In the midst of this, I was interviewing monks about what they thought about these protests, and whether monks had a right or a responsibility as Buddhist monks to participate in them. In other words, I was asking them about the proper place of a religion—Buddhism—in the life of the nation.

Thailand is a predominately Buddhist country, and most Buddhists there follow Theravada Buddhism. This form of Buddhism is commonly associated with mainland Southeast Asia and Sri Lanka, as opposed to Mahayana Buddhism which is associated with East Asia and Central Asia (though the Buddhism of Central Asia is sometimes referred to as Vajrayana Buddhism). Many people view Theravada Buddhism as the form that is closest to the "original Buddhism" taught by Siddhartha Gotama some 2500 years ago. This is partly a scholarly construction, a product of 19th century European concerns with the origins of religions, though it is also the result of the limits of historical (textual and archaeological) evidence from South Asia 2500 years ago. Part of the claims about Buddhism, especially in its Theravada forms, that are embedded in the widespread understanding of the religion is that it is, or is supposed to be, outside of politics. Despite this, Theravada monks (who represent only a fraction of the number of Buddhists) regularly engage in both direct and indirect political activities throughout the Theravada worlds of Southeast Asia and Sri Lanka. These actions open them up to accusations that they are not engaged in "real" Buddhism.

On this particular day in this particular cab, however, I was not talking about politics, but about the images that the cab driver had on his dashboard. In most Bangkok taxis, there would be a combination of amulets, small statues of monks, Buddha images, and occasionally images of gods such as the Chinese Bodhisattva/goddess of compassion, Guanyin, or the elephant headed Hindu god, Ganesh, seen by Thai Buddhists as well as Indian Hindus as the "solver of problems."[1] These amulets and images are usually understood by Thais, taxi drivers and otherwise, as having protective qualities. Drivers will also sponsor monks to draw yantras, magical spells, on the roof of the car above where the driver sits to maximize protection. At the same time, however, in conversations with drivers it became clear that Thais hold a variety of attitudes towards these images and amulets. Some see them as directly efficacious; some have an emotional attachment to the images or amulets, and enjoyed the story of how they came into their possession; others did not really pay much attention to them, because they "belonged" to a driver that they shared the taxi with, or because they did not put much stock in their protective qualities. In other words, even in a country where identity is closely tied up with the Buddhist religion, something that we often call a "world religion," people often vary significantly in how they regard the important aspects of the religion.

1. In the bombing of the Erawan Shrine in August 2015, the shrine was often referred to as "Hindu." While the shrine has a god at its center that is commonly associated with Hinduism, Brahma, it should be seen as a shrine for Thai Buddhists. While Thai Buddhism was influenced by Brahmanical and "Hindu" forms from its earliest days, the reference to these as "Hindu" is an example how European and American observers have difficulties conceptualizing the ways Buddhism incorporates cults that are not seen as "Buddhist." See McDaniel (2011) for some discussion of these issues.

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00039-9

The driver of my cab on this day was the "renter" of the amulets and images,[2] and while he delighted in letting me know the monks that had produced the amulets, and the famous temples (*wat*) that he had gone to, we also began to talk about the relationship of Islam and Buddhism in Thailand and religion as well. In the last decade, relations between Muslims and Buddhists in Thailand have sometimes been fraught primarily because of a conflict in the southern four provinces of Thailand between the state and local Malays. This conflict is alternately described in political, ethnic, or religious terms. The state of relations between Buddhists and Muslims in Thailand has become more tense since 2013 because of events in neighboring Myanmar, where radical Buddhists have attacked Muslims as being illegal aliens within the nation-space (despite the fact that these Muslims, the Rohingyas, have been in Myanmar for generations). Yet when I asked him whether there was a conflict between Buddhism and Islam, he told me, "No, not really, there are problems but they are not really about religion." He continued by making claims about the nature of religion and nonreligion. "All religions are the same; Christianity, Islam, Buddhism, Hinduism: they all teach the same thing, about being good. Actually, I am more concerned about someone with no religion than I am with someone with a different religion."[3]

There are a number of assumptions that were embedded in this conversation that I want to highlight. First and perhaps most importantly, implicit in the taxi driver's statements was the idea that religions are coherent phenomena that can be compared to one another. Buddhism and Islam in this case are the same kind of thing. They are within the context equivalent, but also distinct from one another. Second, there were implicit taxonomies within the conversation about ways of being in this world: one can be religious, and one can be not religious. This is understood to be a choice. Third, although the driver mentioned Hinduism, most Thais when talking about "religion," specifically in the way that the driver did, are referring to one of three religions: Buddhism, the "religion" of roughly 90% of the population, Christianity, and Islam. Thais recognize the existence of other religions, but when they talk about religion as being a "pillar" of the country, along with the "nation" and the king, they mean these three religions. What it does not mean from the viewpoint of most Thais are things like animism or spirit worship practiced by the Hill Tribes of the North and Northeast. They will often recognize these as religions, but they are not the religions of the Thai nation, per se. (At the same time, there are practices embedded within Thai Buddhism, such as the exchange of amulets made by famous monks that overlap with some of the lesser forms of religion—whether these are really religious or corruptions of religion is something of a contested issue within Thailand.[4]) Very little of this was spelled out in our conversation; it was understood and assumed. What makes this interesting is that it was not out of the ordinary. While people's opinions varied—some felt like Buddhism and Islam were in the midst of conflict, for example—this was a conversation that was repeated regularly over the course of 6 months. These were the assumptions that most Thais in 2014 have when they talk about religion (*sāsanā*).

It is in many ways the view that most people have about religion in the early 21st century: one can be religious or not religious, and this is usually though not always a matter of choice; religions are equivalent phenomena that are comparable; and there are legitimate and illegitimate forms, though where a given phenomenon fits on the scale of legitimacy is often implicit rather than explicit. Most of us assume we understand what religion is, but we have only very rarely interrogated those assumptions. Indeed, this assumption might be seen as following the well-known adage about pornography, that we can't say what it is, but we know it when we see it (Sullivan, 2005).

This implicit notion of religion has been a problem for the academic study of religion since it began with the beginning of the social sciences in the latter half of the 19th century. Scholars were, of course, concerned with religion before the end of the 19th century, but much of this interest was either theological or antitheological in nature. The disciplined study of religion external to religious communities principally began as a central part of the formation of the modern university. Indeed, some scholars have observed that "virtually all the novel disciplines that came to flourish [in the development of the modern university in the 19th century] cut their teeth on critical interrogation of religion and things religious" (Lincoln, 2012, p. 131; see also Lincoln, 2003, pp. 57–58). That is to say, sociology, anthropology, political science, and psychology all established their independence in part by making religion their object of study, rather than a part of their methodological assumptions. This has some important implications for our understanding of the history of religion. When we use the term "religion," we are referring to it in distinctly modern ways. By modern I am referring to the events of the last two centuries, specifically the emergence of nation-states within the context of European colonialism, and the modern knowledge systems (of which "religion" is a part) that emerged as a part of this process. The problem with using religion as a descriptor is that not all of the phenomena that we describe using the term "religion" were

2. In Thailand, amulets and images are seen as being sacred, and therefore are objects that are not "bought," but rather "rented" by the person who has possession of them.

3. Personal communication, Bangkok, March 21, 2014.

4. For discussions of the role of amulets in Thai society, see McDaniel (2011) and Pattana (2012).

conceived by the people who lived them as we describe and understand "religion." For example, is it appropriate for us to use the term "religion" to describe the cults of Rome or the different types of official and unofficial religious forms that were present in China before 1911 when the empire fell? We describe these as "religious" in part because they entail rites, rituals, and sacrifices in relation to invisible/spiritual/sacred beings. Yet there are two problems with this. First, there is an implicit differentiation within our notions of religion—religion is a distinct sphere—that was either not present or differently conceived of within the worldview of these actors. Second, definitions of religion often entail either tautologies or deferrals to other equally vague concepts. For example, if we take the Durkheimian definition of religion, that it is a "unified system of rites and beliefs relative to sacred things" (Durkheim, 2001), we must still answer what a "sacred thing" might be.[5]

This chapter is meant to address the diversity and history of religion, and while I will do this to a certain extent, it is perhaps better to think about this as interrogating the assumptions that underlie the possibility of even asking questions about the diversity of religion. That is to say, before we can understand the diversity of human practices with regard to religion, it is necessary to understand what religion is, and how religions have been categorized. While it is beyond the scope of this chapter to fully explore either of these issues, it will be my aim here to provide contours of the important issues at play in both definitions and taxonomies of religion.

Let me first set forward several assumptions that I write this chapter with. The first is an assumption about diversity. Regardless of what religion is, I presume that humans have done everything one can imagine in the context of what we now call religious. They have worshiped and believed in anthropomorphic beings, nonanthropomorphic beings, animals, nature gods, ancestors, devils and demons, other humans (who may or may not be seen as super human). They have sung, danced, eaten, buried, written, carved, thought about, sown, reaped, burned, built, eaten, not-eaten, manipulated their bodies in all sorts of ways, valorized humans, crushed humans, built hierarchies in society, demolished hierarchies (though far less often), and many other things that I do not name here. All of these acts have been done at one time or another in the name of something that we might call religion.[6]

The second assumption is that while religion may be old and impossibly diverse, the term "religion" is not. As will be discussed below, the term "religion" is one that is part of the formation of the modern world in which we live. While we can have arguments about what the modern is and when it began, there was an important transformation in the ways that the English speaking world began to talk about how human societies situated themselves in the world, in relation to the notions of metaphysical reality (that is the "divine" or "sacred"). As a part of this transformation, which was also a part of the development of the knowledge projects of the modern European world over the course of the 19th century, the notions of the secular and religion emerged together, as did both the modern notion of science and the things that we understand to be the sciences. In other words, although humans interacting in some way with the universe is probably as old as human societies, this way of talking about it is roughly two centuries old.

Third, religions are things that are understood by people and governments (though not always scholars) to be a universal aspect of the human. That is to say, all human societies are understood as having religious communities or institutions that are fundamental to what they are.[7] There is a certain irony to this, given the assumption above about the relative newness of the category of religion. Although one might say, following J. Z. Smith (2004, p. 179), that throughout most of the non-European world, "religion is not a native category," it is a category that has been taken up by communities throughout the world. How this happened has varied: it was imposed on some communities; taken up willingly by some, taken up as a necessity of modernization, or taken up as a strategic matter. In other words, even though it was not a native category, it has become a universal one.[8] The universality of the category, or perhaps better the seeming universality of the category obscures local differences in how religion is understood as well as the transformation described in the second assumption.

Fourth, and perhaps most importantly, the category of religion is inextricable from questions of power and the political, even when it is understood as apolitical. Defining religion is a part of a larger discourse on religion. This is the idea that the thing we call "religion" is a distinct and

5. Durkheim (2001, p. 46). Durkheim does define sacred things as "set apart and forbidden." He also continues to talk about "beliefs and practices which unite into one single moral community called a Church, all those who adhere to them."

6. Note too that human communities have done most of these acts outside of "religion" as well.

7. Chidester (1996) discusses how Europeans understood that some of the indigenous peoples of Southern Africa did not have any beliefs or practices that the Europeans recognized as religious. While this was empirically false and the product of assumptions of "savagery," this was also held up as the exception that made the rule that all communities have religions.

8. As Gottschalk (2013, p. 32) puts it: "Although the concepts of *religion* may have not had precedent in many cultures and Western imperialists had a disproportionate role in its global naturalization, indigenous people played their role in local adoptions and adaptations of the notion."

definable aspect of human societies (the thing that makes people trustworthy, according to my Bangkok taxi driver). Not all societies and nation-states have valued religion, but in general religion has been seen as a legitimate form of human activity, at least some forms of it. In calling some activities "religious" and others not (calling them, for example, "superstitious" or "a cult") means that one is engaged in a process of determining what is proper and improper. This is inherently political, resulting in practices that are valorized and those that are denigrated and oppressed within societies.

In what follows, I want to explore the issues behind these assumptions, pointing not so much to the diversity of religious practices through time, but rather to how and why certain groups of actors have defined religion as well as categorized different types of religious practices. I am concerned here with the knowledge projects and practices that make these definitions and taxonomies possible in the first place. In the first parts of the chapter, I will discuss the dynamics and practices of definition and classification. In the latter part of the chapter, I will turn to specific case studies from Asia, examining how "religion" came to be incorporated into East Asia as a category, as well as the role it has played in the governing projects of post-Mao China.

THE PROBLEM OF DEFINING

Defining religion is a surprisingly complicated enterprise. There are several reasons for this. First, it is a meta-category, a term that describes a type of activity that is embedded in cultures and societies, and it is an "anthropological" rather than natural term. It is a term that people, scholars for example, use to describe types of phenomena, not the phenomena itself. People generally do not believe in/practice religion, but rather they believe in/practice specific religions, such as Christianity, Islam, and so forth. This means that the term is an umbrella, a "second-order generic concept" (Smith, 2004, p. 194) used to describe a group of things that must all share some essential nature. Second, determining what this essential nature is has proved to be extremely difficult. "Religion" as a term seeks to describe a vast range of activities and practices, in a diverse set of times and places which are not obviously related to one another. To state the obvious, deciding which of these practices, activities, or thoughts is the essential one has been highly contested. Should we assume, for example, that beliefs in gods, for example, are the essential core of religion, or should it rather be worship of these gods? Even if they are unified by god in my question, there is no single answer to this particular question.

We can see this by comparing several recent textbooks which are introductions either to the study of religion or to the study of world religions. These five textbooks,[9] published between 1995 and 2015, are all directed at undergraduates and normally, but not always, "world religions" classes.[10] There are two points that I want to make about these books, one a matter of definition, and the other a matter of taxonomy. First, all of these introductory textbooks feel it necessary to talk about what religion is before they talk about the specific religions. Significantly, none of them use the same definition, though there are commonalities between the different definitions, and shared influences. For example, Young (2005, p. 4) defines religion as "a human transformation in response to perceived ultimacy." Similarly, Deming (2015, p. 4) sees religion as an "orientation to those things which are of *ultimate* value in a person's life," and specifies that they are "systems of traditions of orientations" such as Christianity and Islam. These texts (and also Ellwood and McGraw who define religion in terms of "the sacred" and "things set apart") share roots in both the work of the Historian of Religion, Mircea Eliade, which emphasized religion as a distinct aspect of human life unlike any other,[11] and the theologian Paul Tillich (1958) who saw the nature of religion as being defined by an attention to what he called "ultimate concerns." Brodd et al. (2013) on the other hand, come out of a more critical anthropological tradition, citing Asad's (1993) argument against the possibility of universal definitions of religion. However, recognizing the need to provide at least a working definition, they stipulate that "Religion is a cultural system integrating teachings, practices, modes of experience, institutions, and artistic expressions that relate people to what they perceive to be transcendent." Ironically, this definition also bears the traces of Clifford Geertz's (1973) highly influential anthropological definition of religion, "Religion as a Cultural System" which is precisely what Asad was critiquing. Aside from the general interest of how to think about what religion is, what is important to recognize here is that there are a number of different intellectual traditions of defining what religion might be, as well as disciplinary traditions (anthropological, phenomenological, theological, and sociological to name the major ones). Some of these

9. The books are Young (2005), Ellwood and McGraw (2005), Oxtoby et al. (2010), Brodd et al. (2013), and Deming (2015). These do not exhaust the market, but are representative of it. Several of these have had more than one edition, with the first edition going back several decades. In the interest of full disclosure, I wrote the Buddhism chapter in Deming.

10. On the development of "world religions" as the category of choice to describe the major religious systems of the world, see Masuzawa (2005). Throughout this chapter, it should be understood that terms like religion, world religions, the sacred, and so forth are always categories the meaning of which is under negotiation (and thus the use of quotation marks).

11. Eliade (1959). In this, Eliade's understanding of religion should be understood as a phenomenological transformation of Durkheimian sociology, borrowing the terminology of the sacred and profane, and emphasizing the set apart nature.

textbooks are focused on concrete forms, such as notions of the divine, while others seek to locate the unities within religion in terms of meaning and the uniqueness of religion.

Despite the lack of unity in defining religion, these introductory textbooks display significant consistency about the religions that they focus on: all of them have Hinduism, Buddhism, Daoism, Confucianism and Shinto (though some in stand-alone chapters, and some combined into the religions of East Asia, or the religions of China and Japan separately), Christianity, Islam, and Judaism.[12] Three of the four have Sikhism and Jainism chapters (and a fourth deals with these religions in the "India" chapter), and they all address "new religious movements" either in stand-alone chapters (four out of the five), or in chapters dealing with Japanese religions, for example). The consistency breaks down after this, and the different books address the complexities raised by non−world religions in different ways. Some talk about "tribal religions" (Ellwood and McGraw, 2005) while some use the category of the "indigenous" (Young, 2005; Brodd et al., 2013; Oxtoby et al., 2010).

In some ways, the patterns visible in these books reflect a consensus which is brought into being as much by institutional and capitalistic concerns as it is by intellectual concerns (Masuzawa, 2005, p. 9).[13] They also, however, reflect real confusion over how to address those religions that have not been considered to be "systems."[14] One might consider several reasons for this, some of which are innocent intellectual problems, others of which are reflective of dynamics of power and racism that have been endemic to the assumptions and concerns of European/American intellectual projects. On the innocent side, the religions of indigenous communities have often been part of disparate communities, rather than unified in empires, and so the consistencies and patterns within them have not always been obvious. Many of them have also not always had a written corpus, but rather oral literature, and while early scholars, missionaries, and colonial officials may have collected what came to be called folk tales, the complexity and profundity of these narratives has not always been obvious, certainly not to the early scholars, missionaries, colonial officials, and sometimes modernizing nationalists, who collected them. Their failures to recognize these patterns is reflective of the negative. The Europeans and Americans who first encountered these communities normally assumed that their traditions and communities were pagans, heathens, or savages. Some of these were theological categories; some reflective of straightforwardly racist attitudes held by Europeans and European Americans.[15] While there were exceptions such as Bartolome de las Casas (1992), most of those Europeans who encountered non-Europeans approached them with a strong sense of racial and civilizational superiority. This much is well known, of course, but it is important to highlight that scholarly ways of conceptualizing the social formations that we call religions bear the genealogical traces of the past. Smith put this concisely when he noted that:

> *A world religion is a religion like ours; but it is, above all, a tradition which has achieved sufficient power and numbers to enter our history, either to form it, interact with it, or thwart it. All other religions are invisible. We recognize both the unity within and the diversity between the "great" World Religions because they correspond to important geo-political entities with which we must deal. All "primitives" by way of contrast, may be simply lumped together as may be so-called "minor religions" because they do not confront our history in any direct fashion. They are invisible. (Smith 2004, p. 169)*

While the authors of these textbooks often try to think through and around these problems when talking about what religion is and choosing what to put into their textbooks, these racial and civilizational ideologies and hierarchies remain embedded in how we think about what we study in Religious Studies.[16]

There is an additional point that needs to be highlighted when talking about the problem of definition: the "essential nature" of religion. Earlier I noted that one of the difficulties of developing a complete definition of religion is that the diversity of phenomena—practices, beliefs, social structures—renders it difficult to determine what is the core aspect of religion. By core here, I mean that aspect of religion that we could talk about as a universal

12. Oxtoby et al. (2010), it should be noted has the religions of the world split into two different volumes. It uses the same introductory material introducing what religion is in both volumes. The volume on "Western Traditions" has Judaism, Christianity, and Islam, as well as Indigenous Religions.

13. In preparing the "Buddhism" chapter in Deming (2015), I was told that textbook companies have an informal "80−20" rule in thinking about textbooks. There could only be about 20% of the book that was considered to be new or different, because otherwise instructors would not be willing to adapt it, because it would change their classes too much.

14. Masuzawa (2005, p. 15), cites a suggestion by Immanuel Wallerstein, that anthropology developed to address "tribal" societies, small in scale, while Orientalism developed to study "large-scale" kingdoms (civilizations or systems) with vast written traditions.

15. Notions of civilizational superiority tied up with notions of religion and civilization are not unique to the Europeans and Americans, but were common within East Asia, particularly in the context of modernization and nation-state formation. See Tanaka (1993) and Dikötter (1992) for Japan and China, respectively.

16. While there have been many efforts to move beyond these ideologies, it can be very difficult to do so, even when scholars are well-meaning. In my first year of graduate school at the University of Chicago, the History of Religion program (the history of which provides the backbone of my narrative in this chapter) finally removed "Primitive Religions" from the title of one of the possible qualifying exams to be taken. This was in 1995.

essence, one that would allow us to understand clearly that the animal sacrifices performed by the emperor of China (or by his attendants) in premodern China, the beliefs/writings of John Calvin or his Presbyterian followers, and the possession practices of *candomblé* in Brazil can all be linked into the same concept: religion. While this has produced a large number of different attempts at defining "religion"—the Historian of Religions, J. Z. Smith (2004, p. 193), cites a textbook from 1912, which by that point had listed over 50 different attempts to define religion—scholars have dealt with this differently. Some, not liking the definitions they found, have come up with their own definitions, emphasizing different parts of the common definitions (see, eg, Tweed, 2006; Deming, 2005 for recent attempts). Others, such as W. C. Smith 50 years ago (1978), have called the term unworkable. For W. C. Smith (among others), the point is not just the diversity, but rather the simple but profound point that "religion" is a European concept that has been introduced, sometimes by force and sometimes by choice to promote modernization, and not really a useful concept for understanding how non-Western societies conceptualize the world.

Among the more powerful critiques regarding the nature of religion was Asad's (1993) critique of Clifford Geertz's Anthropological definition of religion (referred to earlier). Geertz's (1973, p. 90) definition, influential within the study of religion both inside and outside of Religious Studies for almost two decades, defined religion as "a system of symbols which acts to establish powerful, pervasive, and long-lasting moods and motivations in men by formulating conceptions of a general order of existence and clothing these conceptions with such an aura of factuality that the moods and motivations seem uniquely realistic." Geertz's definition was about the production of meaning in societies[17] and was attacked by Asad (1993) on primarily two grounds. The first was an essentially Foucauldian argument that Geertz had failed to account for the role that power played in the constitution of the formulations that Geertz said the system of symbols represented. The second was that Geertz's emphasis was one that privileged interior aspects of social life (beliefs, moods, and motivations), and that this was influenced by the widespread Protestant emphasis on belief as the foundation of religion. Asad argued that while Geertz's definition implicitly at least made claims to being a universal definition, that it could not be because it privileged concerns that were the product of a certain time and place (ie, mid-20th century North American academy, itself the product of the late 19th century development of the modern university). Asad took this a step further to suggest that there could be no universal definition of religion, precisely because all attempts to define religion are the product of specific times and places.

Asad's critique seems to me to be right, up to a point. The category emerged in a particular time and place, and that has shaped the implicit notions that are embedded in the category. There is not likely to be a single definition of religion which can fully account for all things that all societies might want to call religion. However, it is also not enough to simply abandon the category, despite its problems. It is a term that has been naturalized around the world, and is a category embedded within legal structures.[18] Thomas Tweed has suggested that the inability to create a science based on a universal definition should not produce despair, any more than anthropologists should stop talking about "culture" or art historians should stop talking about "art." Religion is a "constitutive category" of the field, and it is the responsibility of the field to continue to struggle with how to think about the term, and to understand the ways in which nonspecialists think about it, both implicitly and explicitly (Tweed, 2006, pp. 30–33). Indeed, as the Historian of Religions Bruce Lincoln (2003, p. 2) puts it, the historically situated nature of "religion" as a category should not render "futile all efforts at definition, however, particularly when one understands these as provisional attempts to clarify one's thoughts, not to capture the essence of things." A disciplined concern and attention to what "religion" is can never be final, but rather shifts according to particular times and places. So let us turn to these attempts a bit more explicitly.

DEFINING RELIGION

In thinking through how best to define religion, scholars have sought to categorize different kinds of religions. These categorizations have to do with the content of the definition, the work of the definition and the form that the definition has taken. While the word religion predates the 16th century, according to Smith (2004, p. 180) it is only at this point that there begins to be something resembling a modern usage of the term. In large part, this is because it is at this point that Europeans encounter on a large scale communities and societies that are so clearly distinct from those that follow Christianity, Islam, or Judaism. For the most part, early efforts to define religion were focused around notions of gods, or more appropriately

17. While Geertz's definition gained prominence with its republication in Geertz (1973), it was first written in 1963, and so follows the phenomenological work of Eliade's (1959) and Berger's (1967) sociological discussions of religion. While they differ in important ways, all of these bear the imprint of post–World WarII/Cold War concerns reflecting existential anxiety and attention to meaning-making.

18. On the way that defining religion in general or specific religions produces unintended consequences within legal systems, see Sullivan (2005) and Sen (2010).

God. Jason Ananda Josephson has argued that these were "theocentric," "implicitly theological and rooted in the assumption that a monotheistic divinity has revealed religion to different cultures." This theocentric notion of religion (which he links to the mid-18th century *Encyclopedie*) was replaced over time by what he refers to as a "hierocentric" notion of religion, based instead on established notions of beliefs defining the relationship between "man and the sacred" (Josephson, 2012, p. 9, citing *Larousse Dictionairre*). This shift happened as a result of a desire to de-Christianize the concept of religion, a task that was only partially successful. At least through the 19th century scholars and government officials in places like China and Japan understood Protestant forms of Christianity to be the principal model of what religion meant. Yet, as the discussion of the definitions of religion in the textbooks discussed above showed, the "hierocentric" notion continues to be influential in the way many define the concept. One of the ironies that Josephson points to is that even as the essence of religion shifted from a focus on God to one on the sacred (an admittedly vague concept that has presented its own problems since Durkheim used it in his definition of religion in the early 20th century), is that the collections of religions that were determined through the "theocentric" model, what we tend to call "world religions" at this point, were simply inherited within "hierocentric" models of religion: "While the *hierocentric* definition seems to represent a rejection of divine revelation in favor of the anthropological concept of the sacred, it inherited a cluster of 'religions' based on the very principle that it ultimately rejected. Even once it discarded the old principle, the new definition was stuck with the pre-established list of religions, which was then used to generate a variety of vague commonalities necessary to formulate a new definition" (Josephson, 2012, p. 11). In other words, efforts to develop definitions or taxonomies of religion following scientific principles have generally been hindered by implicit theological assumptions left over from the point when "religion" was a primarily theological category.

While the shift from the theocentric to hierocentric definitions allowed for the possibility of a de-Christianized notion of religion, it also opened up the possibility of other types of definitions. Martin Riesebrodt has suggested that the primary distinction in determining a model of religion is to decide the difference between "content-based" definitions, like the theocentric ones to which Josephson refers, and functionalist models of religion,[19] which explain the role that religion plays in society. Content-based definitions of religion have sometimes been accused of being too specific (and therefore cannot explain enough of the diversity of religion), or too theological. Riesebrodt argues conversely that functionalist explanations of religion are good for explaining how society works, but they are not particularly good at explaining what religion is or does. They cannot differentiate clearly between religious and nonreligious phenomena, and as a result, everything gets mashed together (Riesebrodt, 2010, pp. 72–73).[20]

Riesebrodt's distinction between content and functional models is described in a different way in Thomas Tweed's effort to develop a theory of religion. Tweed articulates a distinction between "empirical" and "stipulative" definitions of religion. The former seeks to be a "true statement about the way things are"; that is, it is a statement that is either true or false about some object. They purport to provide tools for describing how some object works, or exists. These statements are derived inductively by looking at conditions "on the ground" and using these conditions to develop statements that can be applied to determine whether a phenomena is the same. Riesebrodt's (2010, p. 91) notion of religion, for example, that religions are about "averting misfortune, overcoming crises, and providing salvations" is derived from examining liturgies. He argues that liturgies provide access to actions that people engage(d) in and they also hold clues to the meaning that people gave to their actions. Stipulative definitions, on the other hand, are not the outcome of study, but rather are propositions that begin the study. According to Tweed, they are less about determining the degree of truth or falsehood, but rather their importance is about "usefulness" for understanding the phenomena at hand. In a sense, stipulative definitions (such as Geertz's discussed in the previous section) direct our attention in particular ways to begin the process of analyzing phenomena, whether at the level of the individual or of society. To a certain extent, the difference between these two types of definitions is situational more than qualitative. In other words, the question is not whether one type is better than the other, but rather what kinds of questions one is asking. In other words, the question is whether the scholar wants to understand what religion *is* or what religion *does*.

I will not provide my own definition here. There are a number of accounts that I find compelling that I use in the course of teaching or researching different problems, and the point of this chapter is not to provide a final, universal account of what religion is or does, but rather to explain the contours of how it has worked. There is one other point I want to make about definitions, however. While scholars within the modern university have consistently studied religion over the last 200 years, whether theologically or not, the issue of what "religion" is and does has only been

19. I recognize a slippage in my writing between definitions and models. As Tweed (2006, p. 42) notes, definitions imply theories, so a definition of religion is really a theory of religion.

20. Functionalist definitions often have a hard time explaining the ways that nationalism is or is not a religion, for example.

important at certain moments. For example, in the late 19th century, during the period of high colonialism and faced with the diversity of human practices and the problem of governing them, religion and its essential nature was of central concern.[21] Another key moment was the late 1960s and early 1970s when postwar existentialism and modernization theory encouraged scholars to think about how religion functioned as a fundamental factor of meaning making in human communities.[22] A third moment has been the post−Cold War, during which we have seen the reemergence of religion as a vital force in politics, whether in the break up of Yugoslavia with its ethno-religious wars, the religious right in US politics, or the anxiety over religiously inspired "terror."[23] The problems scholars were concerned with during these moments have been different, but they have been inspired to define and think about the nature of religion at moments when the nature of society is in question, suggesting that religion (or "religion") is at the heart of society.

CLASSIFYING RELIGION AS A PROJECT OF SECULAR MODERNITY

While we might suggest that defining "religion" is a modern project, classifying religion is something that people have done for a very long time, if not throughout history. Often this classification has been little more than a distinction between your religion and my religion, though this has often had a moral valence. J. Z. Smith writes about pre-Columbian Christian taxonomies of religion in this vein. There were four religions: Christianity, Islam, Judaism and Other. These were internal accounts of believers, and as a result, this taxonomy could be glossed as one good, true religion, two traditions that were differently defective, and everything else that did not fit in the first three (Smith, 2004, p. 187). Similarly, from at least the Ming dynasty in the 14th century, the imperial Chinese government differentiated between "official" and "popular" religion. Official forms were those that were prescribed in legal documents and included the many official rites that the emperor was supposed to conduct (such as sacrifices to Heaven and Earth or the imperial Ancestors). Popular religion included a diverse array of cults to individual gods and goddesses, as well as the Buddhists and Taoists that were not regulated by the state (Taylor, 1990, p. 128). This taxonomy was essentially heterogeneous with two categories: orthodox state forms and everything else. At the same time, "everything else" was divided into tolerable and intolerable forms (the latter was referred to "heterodox" or *xiejiao*).[24] There was another important taxonomy within late imperial China that was referred to as the *san jiao*, the "three teachings." The *san jiao*, which referred to Buddhism, Taoism, and Confucianism, was an idea that saw these three religions as unified at their core. This is similar to, but not quite the same as contemporary views of religion. Where in much contemporary understanding, religions are seen (often unreflexively) as being essentially the same type of social phenomena, the *san jiao* were seen as authoritative teachings which differed on the surface, but fundamentally partook of the same essence.[25]

There is an important shift that happens over the course of the 18th and 19th century that affects the way that the classification of religion takes place. This is the development of the idea of the secular, of which religion is a central component. In general terms, the narrative of secularization is a familiar one (perhaps too familiar). After the Wars of Religion and the Peace of Westphalia that followed in the mid-17th century, religion was increasingly relegated to the private sphere. The development, which involved a disembedding of religious ideologies from the public sphere, was a long process that took several hundred years, and indeed has never been a completely realized project (Keddie, 2003, pp. 17, 20). However, in the common narrative as areas of knowledge emerged from the control of church authority, "liberated from the sphere of religion… [n]ew sciences bec[a]me viable and effective as ways of understanding European society" (Masuzawa, 2005, p. 16). As this was taking place, while specific religions remained part of society, the idea of religion as a distinct aspect of society (or indeed human nature) was also emerging (again, Durkheim plays an important part in this). What religion was, as I have already discussed, was not and is not always clear, but there was a clear idea that religion was a distinct phenomenon that itself becomes an object of study. In other words, the very concept of religion, the development of the "isms" we call the world religions, and the idea that these share a common nature, these ideas

21. This can be seen in early anthropologists such as such as E. B. Tylor, who believed in evolutionary models of human cultures and argued that a minimal definition of religion was a "belief in spiritual beings," as well as Orientalists such as Friedrich Max Müller who sought to use philological methods to develop a "science of religions." For discussion of the development of Anthropology and Orientalism and their concern with religion, see Masuzawa (2005, pp. 15−17).

22. See footnote 18 above.

23. It is during this period that we see Asad's (1993) critique of Geertz discussed earlier, as well as a number of scholars critiquing Huntington's (1996) argument about the "clash of civilizations." See also Casanova (1994), Juergensmeyer (2003), and Lincoln (2003).

24. Brook (2009) suggests that there is significant continuity between Qing dynasty (1644−1911) regulation of "religion" and what was implemented within the modern Chinese state. On the reimportation of *xiejiao* as a category of governance by the early 21st century Communist government of China, see Palmer (2008).

25. In this, the idea of the *san jiao* was more like the idea articulated by Max Müller (1870, p. 14) that all religions were reflective of the sacred or divine (this was in the hierocentric mode to use Josephson's terms), and that religion is the human "faculty of apprehending the Infinite."

emerge as a fundamental part of the idea of the secular world (Masuzawa, 2005; Gottschalk, 2013, p. 6).[26]

The classification of religions by European scholars began in earnest in the 18th century, part of the "great urge to classification" that delineated both the religions of the world and classified them according to shared characteristics (Gottschalk, 2013, p. 22). According to Smith (2004, p. 186), this was part of an explosion of data which entered European spheres as a result of colonialism, and classifying religions was a part of an effort to determine if religion should be spoken of in the singular or plural—that is, religion or religions. Scholars developed a number of different models for classifying religions during this period, dividing religions sometimes theocentrically, sometimes according to other criterion.[27] A. M. Fairbairn, for example, divided religions into "Spontaneous or Natural Religions" and "Instituted Religions." Among the former were "Primitive Naturalisms" such as early Greeks, Hindus, or Slavs, and "Transformed Naturalisms" which included Romans, Egyptians, and Ancient Chinese. Another model, developed by Cornelius Petrus Tiele in *Outline of the History of Religion to the Spread of Universal Religions* (1876), organized religions according to the levels that they had attained, dividing religions into "natural religion" and "ethical religions." Natural religions had three branches in Tiele's model: "magical religions under the control of animism"; "purified or organized magical religions"; and "anthropomorphic polytheism." Among the first were "savages and uncivilized peoples"; the second included the Kami of Japan and the Finns; and the last included the Vedic religions. The "ethical religions" in Tiele's account were divided into "race" or "national" religions such as Taoism and Confucianism or Brahmanism and "universalistic religious communities," which included just Islam, Buddhism, and Christianity. In Smith's account, the shift from theocentric to hierocentric models of religion (ie, the shift from god(s) to the sacred or ultimate concerns described earlier) came less from a desire to de-Christianize religion than to grapple with the complexity of the religions that scholars encountered. These 19th century classifications were morphological but not evolutionary; they depended on hierarchical notions and assumptions that religions had attained higher or lower states, but they tended not to be focused on historical change that evolution demonstrates. In many of these models, Christianity (and in particular Protestant Christianity) was either implicitly or explicitly the highest form.

There was another way of classifying religion that became prevalent in the 20th century, which was to think about religion in relation to related but somewhat different terms, such as magic, superstition, spirituality, and science. Like defining religion, there were ways in which this was done prior to the development of secular modernity (such as when the Chinese imperial government declared a movement to be unorthodox), but the relationship between these different categories takes on a particularly important turn with the emergence of secular forms of knowledge (and the self-conscious view that these forms of knowledge are *secular* and "scientific," and not religious). The relationship between magic and religion, for example, was one that scholars explored in a variety of ways in the late 19th and early 20th centuries. While this can be seen as an issue within the models classifying religions above, it took a more specific direction in works like *The Golden Bough* (first written in 1890), James George Frazer's (1959) multivolume study into the nature of magic and religion that human societies naturally progressed from magic to religion to science. Several decades later, the anthropologist Bronislaw Malinowski removed the evolutionary (or perhaps better developmental) framework that Frazer used and talked about magic and religion as serving different functions within "primitive" societies. Instead of progressing from one to the other, magic served as a type of primitive science, while religion provided a community with its meaningful aspects, reintegrating the community after a death, for example (Malinowski, 1992).

There is a pejorative aspect to this, of course, that is related to the unspoken discourse of the secular which is "scientistic," in that scientific ideas are hegemonic, and the language within which knowledge is articulated (Gottschalk, 2013, p. 29; Asad, 1993). Within the context of the secular modern, belief has been privileged over ritual, and science over religion. This took form in the English speaking world as a privileging of the Protestant focus on beliefs over Catholic ritualism.[28] This has not just affected how Protestant forms are described; it has also had a significant impact on how scholars have studied religions like Buddhism as well. There has been a tendency within the study of Buddhism to privilege what are seen as the words of the Buddha over the lives of Buddhists because living Buddhists in Southeast Asia, for example, were often seen as being overly embedded in magical frameworks (Hallisey, 1995). These "protestant presuppositions" (Schopen, 1997) led scholars to presume that the Pali canon of Theravada Buddhism could be read uncritically as

26. Most forms of modernization theory, with the idea that religion will disappear as societies modernize, mistakenly hold that secularization is an inevitable historical process.

27. Information from this section comes from Smith (2004, pp. 186–191, esp. 189–191).

28. Anti-Catholic sentiments in England and the United States are complicated, and are as much about sovereignty and ethnicity as they are about attitudes towards ritual and magic. However, anxiety over ritualistic forms and the magic that is situated within the veneration of saints, for example, should be seen as complementary.

reflecting the world in which the Buddha taught, rather than as an ideological account of how certain followers of the Buddha imagined it.[29] Moreover, early scholars of Buddhism were as likely to see Buddhism as a "philosophy" as a religion, because of its rationalist forms. This meant that phenomena such as the amulets and images in my Bangkok taxi cab were seen as "corruptions" of the rational philosophy of the Buddha. In recent decades, however, in line with the turn to the "quotidian" (Tweed, 2015), scholars have argued rightly that practices that are negatively referred to as "magical" are central to Buddhist worlds (see, eg, McDaniel, 2011).

The concept of religion should thus be seen not as a single concept, but rather one that is in relationship with other concepts. Peter van der Veer has suggested that we see "religion-magic-secularity-spirituality" as a "syntagmatic chain," a series of terms that are "connected, belong to each other, but cannot replace each other. They do not possess stable meanings independently from one another and thus cannot be simply defined separately. They emerge historically together, imply one another, and function as nodes within a shifting field of power" (van der Veer, 2014, p. 9). These concepts, to which we should also add science and superstition,[30] are often also hierarchically oriented and sometimes have a moral valence as well. Thus "religion" is superior to "magic" or "superstition" but inferior to "science" and sometimes "spirituality."[31]

THE DEVELOPMENT AND USE OF "RELIGION" IN EAST ASIA IN THE 19TH AND 20TH CENTURIES

In this last section, I want to turn to several different aspects of how religion has developed in Asian communities over the past 150 years. This has not been a straightforward process and has entailed both the appropriation and imposition of the categories of religion, superstition, science, etc. onto the religious worlds of communities throughout Asia. Often a top-down process, it has deeply impacted how people conceptualize and live their religions. While religions have been present within Asia for many centuries, the conceptual framework of religion was not. Indeed, religion was a word that was not present in the modern sense of the word in Asia prior to colonialism (for the majority of Southern Asia, colonialism begins in the latter part of the 18th century; for East Asia, it is from the mid-19th century). While it is now a concept that has been fully indigenized, this was a process that took decades. It began with the need to invent a word; in some places this was done by modifying an existing concept. For example in Hindi, "religion" is the word *dharma*. Prior to the modern era, *dharma* had many meanings, such as "truth," "law," and "duty." Many of these meanings have resonances with the ways that religion can be defined (and indeed some of these meanings for *dharma* can still be attested to). Similarly, some Southeast Asians such as Thais and Khmer who followed Theravada forms of Buddhism appropriated the word *sasana*, which classically has meant "the teachings of the Buddha," to designate "religion." In East Asia, scholars and officials took a different direction, using a fairly obscure Chinese Buddhist term and repurposing it to mean "religion." This was done in Japan first, in an effort to translate treaties into Japanese, using the term *shukyo* (Josephson, 2012). Somewhat later in the midst of their own modernization and efforts to oppose colonialism, Chinese scholar/officials reappropriated this term, using a Chinese reading (*zongjiao*).

"Religion," whether *shukyo*, *zongjiao*, *sasana*, or *dharma*, has now been fully indigenized throughout Asia, and it now has a fairly stable meaning, even though the connotations may vary across the region. However, this was not the case in the latter decades of the 19th century and early 20th century. Not only was this a new word and concept that was imported into the region, but it was also unclear exactly what was the phenomena to which it referred. This uncertainty was relevant in at least two different ways. First, while Christianity was the primary model for the term, for the first half of the 20th century, and particularly in the 1920s, Chinese scholars debated what the term meant and which aspects of Chinese culture it governed. According to the scholar/official in question, *zongjiao* might mean Christianity, a positive ideology at the heart of the nation, or superstition (in the sense of a false ideology or science). Indeed, it was only after the Communist victory in 1949 that the last sense of religion became stable in the use of the word. Second, to the degree that there were several different religions in Asia, it was not clear which of these could be accurately described using the term *zongjiao*. The clearest example of this in China was whether or not Confucianism was to be understood as a religion. In the European and American academies of the late 19th century, Confucianism was widely understood to be an example of a religion, but this was not as clear to Chinese people, and certainly not to the Qing government. During the Parliament of World Religions in Chicago in 1892, a representative of the Qing government came to speak about Confucianism. Peng Guangyu, the First

29. This should not be taken as a pejorative statement about the Buddhist texts. Rather it is a statement that they are interested and foster a particular position about the nature of reality. While they can provide clues to conditions in early Buddhist communities, they should not be read as historical accounts (according to historical disciplines) any more than the gospels of the Christian Bible should be read as reflecting historical experience.

30. In China, in the 1920s, for example, modernizers and nationalists often saw religion/tradition as an impediment to the development of Modern China, precisely because it was seen in opposition to science.

31. On spirituality, see Huss (2014).

Secretary of the Legation of the Qing government in Washington, DC, argued that Confucianism was not a *zongjiao* (religion), but rather an authoritative teaching (*jiao*) about the proper human relations between ruler and subject (van der Veer, 2014, p. 86). Moreover, he denied the legitimacy of the concept of the *san jiao* which linked Buddhism, Taoism, and Confucianism, rejecting not the metaphysical aspects of Confucianism, but that these should be understood as a "religion" or equivalent to other such teachings. Several years later, however, one of the most important officials of the Qing government, Kang Youwei, sought to recast Confucianism as a religion along the lines of Protestant Christianity, in part because he believed that powerful nations had religions at their roots and that the way for the Qing to resist Western imperialism was to reform the national ideology (Sun, 2013, pp. 21–22; see also Pfister, 2015). That these reforms failed is incidental to the fact that how to label the nature of Confucianism was and indeed is a matter of debate among people in the Chinese sphere (including not just the People's Republic, but Taiwan, Hong Kong, and Singapore, as well as the Chinese diaspora in Europe and North America).

The indigenization of "religion" in Japan during the same period is comparable in broad terms, but it entailed a different outcome. When Japan was forced to accept relations with European and American powers in the 1850s, this precipitated the fall of the Tokugawa Shogunate (1600–1868). The Tokugawa had used things we call religion effectively for more than two centuries to control the population and reinforce its authority. Their tools were primarily Confucian ideologies focused on social hierarchy and state authority, and also compulsory affiliation with Buddhist temples. The fall of the Tokugawa Shogunate and the rise of a nationalist imperial government with the Meiji emperor as the head of state led in turn to a disestablishment of Buddhism from the national government. *Shukyo* initially emerged as a concept because Western powers sought to establish freedom of religion, so that Christian missionaries could engage in mission activities (Josephson, 2012). However, the category was actively taken up by Japanese nationalists (along with other terms like "technology" and "science") who believed they needed these concepts to modernize the nation and resist colonialism. Later in the century, the Meiji government sought to use religious ideologies to foster national construction, in particular Shinto (for the same reason that Kang Youwei sought to make Confucianism a state religion in China a few years later). Yet in a bit of legerdemain, the Meiji government determined in 1882 that Shinto had two parts, "shrine Shinto" and "sect Shinto." The shrines of shrine Shinto were state institutions and declared to be about the nation, not religious (Earhart, 2004, p. 167). The upshot of this was that the Meiji government used a "political religion" (Gentile, 2006) as its mobilizing force, but because it was not a "religion" in ways that resembled Christianity, the government could still declare that it supported "freedom of religion."[32]

The way in which "religion" is handled within the Reform-era People's Republic of China (PRC; 1979–present) is perhaps more telling of the complexities that I have been discussing. While the Chinese Communist Party (CCP) is formally opposed to religion, since the end of the Mao era, they have generally recognized that it is better to try and regulate religion than it is to extirpate it, the primary policy goal during the Cultural Revolution (1966–1976).[33] In the past 45 years, there have been swings back and forth, but in general, the Party-State has tolerated what it calls "normal religion." Normal religions in China include Buddhism, Taoism, Christianity, Islam, and Catholicism, and people are allowed to practice these religions openly as long as this is done in registered places at registered times.[34] This does not exhaust religious practice in China however. There is a vast ocean of popular religious practice that does not easily fall under the designation of "normal religion"; this is sometimes, though not always referred to as "feudal superstition" (*fengjian mixin*). Part of the CCP's regulatory efforts have been based on manipulating the definition of religion to its own ends. In 1978, the CCP declared, "All worship of supernatural forces can be called superstition. Religions are superstition, but it cannot be said that all superstitions are religions. For example, no kinds of feudal superstitions are religions" (Lancashire, 1981, p. 277). The CCP has over the years used this definition as a mechanism of control. Essentially what counts as "religion" and what counts as "superstition" (or worse as an "evil cult") varies according to how the CCP perceives its needs. Interestingly, though, occasionally these definitions can provide cover for religious practitioners. For example, popular religious groups, which fall into a grey zone of regulation, have sometimes sought to have themselves redefined as "Taoist" or as "Buddhist" so that they are given a legal standing. This entails some tradeoffs, though, because once they are registered as such, they are no longer vulnerable to political movements against "superstition," but they are subject to greater regulatory scrutiny (Chau, 2009).

32. It is perhaps worth noting that this distinction that shrine Shinto was not religious was largely disbelieved by non-Japanese, and is specifically rejected in the "peacetime" Constitution imposed by the United States after World War II.

33. For a clear articulation of the CCP's post-Mao policy, see "Document 19: The Basic Viewpoint and Policy on the Religious Question during Our Country's Socialist Period" (MacInnis, 1989, pp. 8–25).

34. The policy has relaxed over time, but it is not clear that it is a fully liberalizing one. As Pitman Potter (2003) put it, there is still a significant "belief in control."

CONCLUDING THOUGHTS

Why does this matter in relation to my taxi driver in Bangkok? He was articulating a position that is not uncommon, and that would seem to be exactly what we would expect. Religion is about ethics, about being good, and there are two types of people: religious and not religious. This does not really seem to say anything about the history and diversity of religion. To the contrary, however, what this man was articulating to me in the spring of 2014 was precisely the product of the last century and a half, of the formation of the secular, and the idea that "religion" is a natural category that articulates certain kinds of actions and attitudes. My point is not that this is an unreasonable thing to think (or rather not to think, because it was not something that he had to think about). Rather, it is that this is a relatively new attitude, and that coming to think this way is an effect of processes of governance, education, and the wider development of the world in which we live. Rather than seeing things as true or not true, we have come to see religions as a series of similar phenomena that we have a choice about.

Not everyone thinks about "religion." Indeed, most people do not; rather they pay attention to the ways that their own specific religion develops, and perhaps is perceived. For the vast majority of insiders, the salient categories are not different types of religions, but rather religion/not-religion (like my taxi driver) or the moral variation within the syntagmatic chain of religion-magic-superstition-science. Those that do think about "religion" have been primarily scholars and state actors, the former presumably to understand society and the latter to govern and/or control it. While these are different kinds of projects, it should be clear from what has been said that these projects sometimes overlap. Scholars in the human sciences were deeply involved in colonial projects up through the end of European colonialism. Indeed, in important ways, scholarship about religion is the very product of the colonial enterprise (Gottschalk, 2013), just as anthropology developed in the need to understand (and control) the peoples that were colonized (Masuzawa, 2005). This overlap of state and scholarly projects has persisted through the Cold War (Wax, 2008; Ford, 2012), and indeed into the post−Cold War era, including the "Human Terrain System," the US Department of Defense's efforts to use Anthropologists in the "war on terror." Scholars have of course been critical of these efforts, just as they have taken part in them.

The point is that the concept of religion is inevitably framed by politics. This chapter has sought to argue that before discussion of diversity of religious practices and institutions begins, the way in which religion is understood has to be interrogated. Religious practices and communities are not always political in nature; indeed sometimes they are apolitical or even antipolitical. However, the nature of religion, the assumptions around the category, the concepts that are part of its web of relations, what counts as religion, and how those definitions and classifications are implemented through scholarly and/or popular discourse or governing practices are inevitably shaped by the politics of the day.

REFERENCES

Asad, T., 1993. Genealogies of Religion. Princeton University Press, Princeton, NJ.

Berger, P., 1967. The Sacred Canopy: Elements of a Sociological Theory of Religion. Doubleday, Garden City, NY.

Brodd, J., Nystrom, L.L.B., Platzner, R., Shek, R., Stiles, E., 2013. Invitation to World Religions. Oxford University Press, New York.

Brook, T., 2009. The politics of religion: late-imperial origins of the regulatory state. In: Ashiwa, Y., Wank, D. (Eds.), Making Religion, Making the State. Stanford University Press, Stanford, CA.

Casanova, J., 1994. Public Religions in the Modern World. University of Chicago Press, Chicago.

Casas, B., 1992 [1552]. In: Stafford Poole, C.M. (Ed.), Defense of the Indians. Northern Illinois University Press, DeKalb, IL.

Chau, A., 2009. Expanding the space of popular religion: local temple activism and the politics of legitimation in contemporary Rural China. In: Ashiwa, Y., Wank, D.L. (Eds.), Making Religion, Making the State: The Politics of Religion in Modern China. Stanford University Press, Stanford, CA.

Chidester, D., 1996. Savage Systems: Colonialism and Comparative Religion in Southern Africa. University of Virginia Press, Charlottesville, VA.

Deming, W., 2005. Rethinking Religion: A Concise Introduction. Oxford University Press, New York.

Deming, W. (Ed.), 2015. Understanding the Religions of the World: An Introduction. Wiley Blackwell, West Sussex, UK.

Dikötter, F., 1992. The Discourse of Race in Modern China. Stanford University Press, Stanford, CA.

Durkheim, E., 2001. Elementary Forms of the Religious Life. Oxford University Press, Oxford.

Earhart, B., 2004. Japanese Religion: Unity and Diversity, fourth ed. Wadsworth, Belmont, CA.

Eliade, M., 1959. The Sacred and the Profane: The Nature of Religion. Harcourt Brace Jovanovich, San Diego, CA.

Ellwood, R.S., McGraw, B.A., 2005. Many Peoples, Many Faiths: Women and Men in the World Religions, eighth ed. Pearson/Prentice Hall, Upper Saddle River, NJ.

Ford, E., 2012. Cold War Monks: An International History of Buddhism, Politics and Regionalism in Thailand and Southeast Asia 1941−1976 (Ph.D. dissertation). Yale University.

Frazer, J.G., 1959. In: Gaster, T.H. (Ed.), The New Golden Bough. Criterion Books, New York.

Geertz, C., 1973. The Interpretation of Cultures: Selected Essays. Basic Books, New York.

Gentile, E., 2006. Politics as Religion. Princeton University Press, Princeton, NJ.

Gottschalk, P., 2013. Religion, Science and Empire: Classifying Hinduism and Islam in British India. Oxford University Press, Oxford.

Hallisey, C., 1995. Roads taken and not taken in the study of Theravada Buddhism. In: Lopez, D. (Ed.), Curators of the Buddha: The Study of Buddhism Under Colonialism. University of Chicago Press, Chicago, IL.

Huntington, S.P., 1996. The Clash of Civilization and the Remaking of the World Order. Simon & Shuster, New York.

Huss, B., 2014. Spirituality: the emergence of a new cultural category and its challenge to the religious and the secular. Journal of Contemporary Religion 29 (1), 47–60.

Josephson, J.A., 2012. The Invention of Religion in Japan. University of Chicago Press, Chicago.

Juergensmeyer, M., 2003. Terror in the Mind of God: The Global Rise of Religious Violence. University of California Press, Berkeley.

Keddie, N., 2003. Secularism and its discontents. Daedulus 132 (3), 14–30.

Lancashire, D., 1981. Chinese Essays on Religion and Faith. Chinese Materials Center, San Francisco.

Lincoln, B., 2003. Holy Terrors. University of Chicago Press, Chicago.

Lincoln, B., 2012. The (Un)discipline of religious studies. In: Gods and Demons, Priests and Scholars: Critical Explorations in the History of Religions. University of Chicago Press, Chicago.

MacInnis, D.E., 1989. Religion in China Today: Policy and Practice. Orbis Books, Maryknoll, NY.

Malinowski, B., 1992 [1948]. Magic, Science and Religion and Other Essays. Waveland Press, Prospect Heights, IL.

Masuzawa, T., 2005. The Invention of World Religions, or, How European Universalism Was Preserved in the Language of Religion. University of Chicago Press, Chicago.

McDaniel, J.T., 2011. The Lovelorn Ghost and the Magical Monk: Practicing Buddhism in Modern Thailand. Columbia University Press, New York.

Müller, F.M., 1870. Lectures on the Science of Religion.

Oxtoby, W.G., Amore, R.C. (Eds.), 2010. World Religions: Eastern Traditions, third ed. Oxford University Press, Oxford.

Palmer, D., 2008. Heretical doctrines, reactionary secret societies, evil cults: labeling heterodoxy in twentieth-century China. In: Yang, M. (Ed.), Chinese Religiosities: Afflictions of Modernity and State Formation. University of California Press, Berkeley.

Pattana, K., 2012. Mediums, Monks and Amulets: Thai Popular Buddhism Today. Silkworm Books, Chiang Mai, Thailand.

Pfister, L., 2015. A modern ruist religious vision of a global unity: Kang Youwei's Utopian vision and its humanistic religious refraction in European sinology. In: Jansen, T., Klein, T., Meyer, C. (Eds.), Globalization and the Making of Religious Modernity in China: Transnational Religions, Local Agents and the Study of Religion, 1800-Present. Brill, Leiden.

Potter, P., 2003. Belief in control: regulation of religion in China. In: Overmyer, D. (Ed.), Religion in China Today. Cambridge University Press, New York.

Riesebrodt, M., 2010. The Promise of Salvation: A Theory of Religion. University of Chicago Press, Chicago.

Schopen, G., 1997. Archeology and protestant presuppositions in the study of Indian Buddhism. In: Bones, Stones and Buddhist Monks: Collected Papers on the Archeology, Epigraphy, and Texts of Monastic Buddhism in India. University of Hawai'i Press, Honolulu.

Sen, R., 2010. Articles of Faith: Religion, Secularism and the Indian Supreme Court. Oxford University Press, Delhi.

Smith, W.C., 1978. The Meaning and End of Religion. Harper and Row, San Francisco.

Smith, J.Z., 2004. Religion, religions, religious. In: Relating Religion: Essays in the Study of Religion. University of Chicago Press, Chicago.

Sullivan, W.F., 2005. The Impossibility of Religious Freedom. Princeton University Press, Princeton, NJ.

Sun, A., 2013. Confucianism as a World Religion: Contested Histories and Contemporary Realities. Princeton University Press, Princeton, NJ.

Tanaka, S., 1993. Japan's Orient: Rendering Pats into History. University of California Press, Berkeley.

Taylor, R., 1990. Official and popular religion and the political organization of Chinese society in the ming. In: Liu, K.C. (Ed.), Orthodoxy in Late Imperial China. University of California Press, Berkeley.

Tillich, P., 1958. Dynamics of Faith. Harper, New York.

Tweed, T., 2006. Crossing and Dwelling. Harvard University Press, Cambridge, MA.

Tweed, T., 2015. After the quotidian turn: interpretive categories and scholarly trajectories in the study of religion since the 1960s. The Journal of Religion 95 (3), 361–385.

Veer, P.v.d., 2014. The Modern Spirit of Asia: The Spiritual and the Secular in China and India. Princeton University Press, Princeton, NJ.

Wax, D. (Ed.), 2008. Anthropology at the Dawn of the Cold War: The Influence of Foundations, McCarthyism and the CIA. Pluto Press, London.

Young, W.A., 2005 [1995]. The World's Religions: Worldviews and Contemporary Issues. Pearson Prentice Hall, Upper Saddle River, NJ.

Chapter 40

Religion Viewed From Different Sciences

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WHAT IS SCIENCE AND WHAT IS RELIGION?

When speaking of science, people often have very different connotations and denotations in mind. Most agree that physics and chemistry are sciences. But what about psychoanalysis, to just mention one case of disagreement? Even certain parts of the life sciences are questioned by some as deserving to be called science. Then there are some so-called sciences that are hardly experimental—with astronomy on one side and paleontology at the other end. Apparently, there is a great deal of disagreement as to what science entails. Some say it is a systematic enterprise that builds and organizes knowledge in the form of testable explanations and predictions. Others have a broader conception which embraces all knowledge of the type that can be rationally explained and reliably applied.

So, which are the fields then that should qualify to be called "science"? I am not going to be the judge in this case. Who can anyway? In this article, I will limit myself to the so-called "hard" sciences or "natural" sciences such as physics, chemistry, and biology—because they are often seen as hostile or even lethal to religion. (But something similar could also be said about psychology, to name just another field.) I will not give in to the temptation of crafting a comprehensive definition of science.

It should not be surprising that there is even more controversy when it comes to religion. A very broad definition considers religion as an organized collection of beliefs, cultural systems, and world views that relate humanity to an order of existence. It is a definition that is typically used in religious study courses; it is basically a sociological definition (Geertz, 1993). Then there are psychological definitions in terms of spirituality and self-transcendence (eg, Cloninger, 2004).

My problem with these kinds of definitions is that religion is reduced to some form of cultural or social system. It is like studying science as a (merely) sociological or psychological phenomenon—a set of convictions, rules, and problem-solving techniques. Names that come to mind are Robert K. Merton, Thomas S. Kuhn, and Stephen E. Toulmin. What these approaches have in common is that they ignore, or even deny, that science is (also) about a reality beyond the system of science. In a similar way, religion too refers to something beyond the belief system of religion. What almost all religions have in common is that they refer to (the existence of) a Transcendent Being, usually called God. It is hard to deny that this entails a factual statement—either God is or God is not, either God exists or God does not exist. If God does not exist, our facts are wrong. Therefore, my choice definition is as follows: Religion is about transcendence and about the transcendent one, God—more in specific about a relationship between Creator and creature. I will come back to this definition later.

The question we have to deal with now is whether science leaves any room for religion in the sense just described.

THERE WOULD BE NO ROOM FOR RELIGION, IF SCIENCE COVERS ALL THERE IS

Is there room for religion if religion refers to a transcendent Being? Obviously not, if we take the position that science covers all there is. If transcendence refers to the aspect of God's nature and power that is totally independent of the material universe, beyond all physical laws, then transcendence—or more precisely the *object* of transcendence—is per definition beyond the reach of empirical or experimental science, and therefore

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00040-5

illegitimate, since science is supposed to cover *all* there is. I am not talking here about a *belief* in transcendence, for beliefs can be studied by sociologists, psychologists, historians, and the like. So, if science does cover all there is, then transcendence—and therefore religion, in the definition mentioned earlier—is out of the question. But this conclusion hinges on a questionable presupposition—namely, that science in fact covers all there is.

The view that science is all-comprehensive in covering all there is has become rather prevalent nowadays and is usually called *scientism*. It has been defined as "the view that the characteristic inductive methods of the natural sciences are the only source of genuine factual knowledge and, in particular, that they alone can yield true knowledge about man and society" (Bullock and Trombley, 1999). Scientism is widespread in scientific circles. It is one of the main reasons why some scientists reject the validity and truth claims of religion. Therefore, scientism deserves closer scrutiny.

Supporters of scientism claim that science provides the only valid way of finding truth. They pretend that *all* our questions have a scientific answer phrased in terms of particles, quantities, and equations. Their claim is that there is no other point of view than the "scientific" world-view. They believe there is no corner of the universe, no dimension of reality, no feature of human existence beyond its reach. In other words, they have a dogmatic, unshakable belief in the omnicompetence of science.

A first reason for questioning the viewpoint of scientism is a very simple objection: those who defend scientism seem to be unaware of the fact that scientism itself does not follow its own rule. How could science ever prove all by itself that science is the only way of finding truth? There is no experiment that could do the trick. Science cannot pull itself up by its own bootstraps any more than an electric generator is able to run on its own power. So, the truth of the statement "no statements are true unless they can be proven scientifically" cannot itself be proven scientifically. It is not a scientific discovery but at best a philosophical or metaphysical stance. It declares everything outside science as a despicable form of metaphysics, in defiance of the fact that all those who reject metaphysics are in fact committing their own version of metaphysics.

A second reason is that a method as successful as the one science provides does not disqualify any other methods. Scientism poses an exclusive claim that can only be made from outside the scientific realm, thus grossly overstepping the boundaries of science. If it is true, it becomes false. It steps outside science to claim that there is nothing outside science and that there is no other point of view—which does not seem to be a very scientific move. The late University of California at Berkeley philosopher of science Paul Feyerabend (1975) comes to the opposite conclusion when he says that "science should be taught as one view among many and not as the one and only road to truth and reality."

A third reason for rejecting scientism is the following. Scientific knowledge does not even qualify as a superior form of knowledge; it may be more easily testable than other kinds, but it is also very restricted and therefore requires additional forms of knowledge. Mathematical knowledge, for instance, is the most secure form of knowledge but it is basically about nothing. Consider the analogy used by Edward Feser (2014): A metal detector is a perfect tool to locate metals, but that does not mean there is nothing more to this world than metals. Those who protest that the analogy is no good, on the grounds that metal detectors detect only part of reality while physics detects the whole of it are simply begging the question again, for whether physics really does describe the whole of reality is precisely what is at issue. An instrument can only detect what it is designed to detect. That is exactly where scientism goes wrong: instead of letting reality determine which techniques are appropriate for which parts of reality, scientism lets its favorite technique dictate what is considered "real" in life—in denial of the fact that science has purchased success at the cost of limiting its ambition.

To best characterize this restricted attitude, an image used by the late psychologist Abraham Maslow (1966) might be helpful: If you only have a hammer, every problem begins to look like a nail. So, instead of idolizing our "scientific hammer," we should acknowledge that not everything is a "nail." Even if we were to agree that the scientific method gives us better testable results than other sources of knowledge, this would not entitle us to claim that only the scientific method gives us genuine knowledge of reality. Admittedly, it is true that if science does not go to its limits, it is a failure, but it is equally true that, as soon as science oversteps its limits, it becomes arrogant—a know-it-all.

A fourth argument against scientism is that the pioneers of science were very much aware of the fact that there is more to life than science. When the *Royal Society of London* was founded in 1660, its members explicitly demarcated their area of investigation and realized very clearly that they were going to leave many other fields untouched. In its charter, King Charles II assigned to the fellows of the Society the privilege of enjoying intelligence and knowledge, but with the following important stipulation "provided in matters of things philosophical, mathematical, and mechanical."[1] That's how the "division of the estate" was executed; it was this "partition" that led to a

1. The *Royal Society* originated on November 28, 1660, when 12 men met to set up "a Colledge for the promoting of Physico-Mathematicall Experimentall Learning." Robert Hooke's draft of its statutes reads literally: "The Business and Design of the Royal Society is: To improve the knowledge of natural things, and all useful Arts, Manufactures, Mechanik practices, Engyries and Inventions by Experiments − (not meddling with Divinity, Metaphysics, Moralls, Politicks, Grammar, Rhetorik, or Logic)."

division of labor between the natural sciences and other fields of human interest. By accepting this separation, science bought its own territory, but certainly at the expense of inclusiveness; the rest of the "estate" was reserved for others to manage. On the one hand, it gave to scientists all that could "methodically" be solved by counting and measuring. On the other hand, these scientists agreed to keep their hands off of all other domains—religion, education, legislation, justice, ethics, and what have you.

If the previous objections against scientism are valid, we must come to the conclusion that religion can still stand tall next to science, unless…

THERE WOULD BE NO ROOM FOR RELIGION IF THERE IS ONLY "MATTER" IN THIS UNIVERSE

This centuries-old view has commonly been dubbed *materialism*. It holds the view that all things are composed of material ("matter"), and all phenomena—including consciousness and love, to name just a few—are considered to be the result of material interactions. Not only does materialism assert that matter is everywhere, but also that matter is *all* there is. In other words, matter is supposedly the only entity in this universe; and thus physical matter has been declared the only fundamental reality in this universe. Put in a nutshell, all things are composed of matter and dust, or are the mere result of material interactions.

Materialism is often associated with reductionism, according to which the objects or phenomena individuated at one level of description must be explicable in terms of the objects or phenomena at a lower level of description. This kind of reductionism frequently leads to popular statements like these: an organism is really nothing but a bag of genes; a human being is nothing but a string of DNA; human beings are nothing but specks of dust; human beings are nothing but machines made of meat; human values are nothing but the outcome of natural selection; thinking is nothing but a series of firings along neurons; a human being is only a bundle of instincts; love is nothing but a chemical reaction; religion is nothing but a set of emotions or even illusions. In general, all the previous statements have one thing in common: the whole is nothing but the sum of its material parts. C. S. Lewis (1980) famously dubbed this as "nothing-butery."

What might be wrong with materialism, and its cousin, reductionism? First of all, reductionism has an undisputed preference for lower levels. But one could question why explaining phenomena at "higher" levels, by referring to entities at "lower" levels, could not be turned around by explaining "lower" levels in terms of "higher" levels. The late biologist Barry Commoner (1964) rightly noted that the statement "the secret of DNA is life"—with all its complexity of cellular organization—is at least as compelling as the more popular slogan "the secret of life is DNA."

Secondly, we are dealing here with a metaphysical stance again. For some enigmatic and ironic reason, materialism has quite a spiritual appeal to it. It is one thing to use a sound methodology of searching for material explanations, but it is something else to change such a technique into a doctrine claiming there are no other explanations than material explanations. Materialism is at best a presupposition of scientists, but cannot possibly be a conclusion based on empirical research.

A third problem arises from the following question: what is it that gives matter such a powerful metaphysical position? Materialism does not explain why our universe is the way it is, or why it even exists at all. The cosmologist Stephen Hawking (2002) once worded this as follows: "You still have the question: why does the universe bother to exist." As a matter of fact, our universe need not be the way it is, and it need not even exist (it is only in the dialectical materialism of Marxism that matter is considered to be the absolute). Choosing the option that there just *is* no explanation is basically an *irrational* response that leaves us stuck in a purely material, actually absurd universe. Take the law of gravity—it may help us explain things, but it cannot explain itself. Those who embrace materialism cannot avoid the question as to how matter can ever explain itself, its own existence. Matter cannot just pop up out of nothing; nothing comes from nothing, as the saying goes. Since I do not see how matter could ever explain itself, a solely material universe is essentially an absurd, irrational, and unexplainable universe, which is a stance that defies rationality.

Another reason for rejecting materialism is that it leads to contradictions. The very idea that "nothing exists except matter" is self-refuting because, if it were true, neither it nor any other mental idea or claim would or could exist; so it would deny its own existence. Those who deny the existence of anything nonmaterial also deny the existence of their very own denial since denials are certainly immaterial as well. Claims like these just defeat and destroy themselves, for they cut off the very branch that the person who makes such claims is—or actually was—sitting on.

One of the consequences of this objection is the need for making a distinction between mental activities and neural activities. We cannot just deny the mental, because denying the existence of mental activities is in itself a mental activity, and thus would lead to contradiction. If the mental were the same as the neural, thoughts could never be true or false, as neural events simply happen, and that is that! This is the paradox that the late British biologist J. B. S. Haldane (1928) worded as follows: "If my

mental processes are determined wholly by the motions of atoms in my brain, I have no reason to suppose that my beliefs are true… and hence I have no reason for supposing my brain to be composed of atoms." The famous philosopher Thomas Nagel (2012) asserted that a materialist conception of nature is almost certainly false, except for those who deny that the mental is an irreducible aspect of reality.

This leads yet to another objection against the world view of materialism: Almost everyone—including most scientists—acknowledge that, separate from the material world, there is also an immaterial world. Almost every scientist accepts entities such as scientific laws and scientific statements, hypotheses and theories, truths and falsehoods, all of which are nonmaterial entities. Curiously enough, all scientific explanations based on laws of nature are actually strange entities—they explain material things and events by using nonmaterial laws of nature such as the law of gravity. Unlike all material things surrounding us, laws of nature do not have any of the features that apply to the material world. A law is not located somewhere in space, not even in our minds, for the mind just has a mental picture of the law—yet a law holds everywhere in this universe. It is also beyond time, a timeless entity that cannot emerge nor perish in the history of the universe. Neither are laws of nature subject to change, for they will always remain true, even before they were discovered. Suddenly, we find ourselves in a nonmaterial world where things are not large or small, light or heavy, hard or soft, but instead true or false, and right or wrong. Scientific statements can be true or false, but the things they are about—quarks, atoms, molecules, cells, hormones—are physical or material, but never true or rational. How could there be truth to what science claims if everything were merely material? If this question is answered in the affirmative, then there must be more than what science is about.

It has become increasingly hard to deny that laws are not something material, a mere brain wave or so, but rather immaterial—call them mental, spiritual, or whatever. I am reluctant to call them mental as that adjective might suggest they only exist in our minds (à la David Hume). On the contrary, they are very "real" and exist outside the mind. We may know them but we cannot create them; they are there even before we know them. That is the reason why a bridge designed according to the right laws does stand firm, whereas another bridge collapses because its engineers erred in their calculations or used the wrong laws. That is also the reason why laws of nature have to be discovered, not invented. Without such "given" laws, our minds would not be able to tell true from false and right from wrong.

If you agree with these objections, religion can still stand tall next to science, unless…

THERE WOULD BE NO ROOM FOR RELIGION IF SCIENCE CAN EXPLAIN RELIGION AWAY

There have been many scientific—or arguably semi-scientific or quasiscientific—attempts to explain religion away. Probably the best-known example is declaring religion an "illusion"—as Sigmund Freud would call it—or a "delusion"—as Richard Dawkins (2008) describes it. Did these people effectively refute religion?

First of all, if Freud claims that basic beliefs are the rationalization of our deepest wishes, would this not also entail that his own atheistic beliefs could be the rationalization of his own desires as well? Second, even if belief in God were wishful thinking, one could never prove that it is nothing more than wishful thinking, for the simple reason that absence of evidence is not evidence of absence. Third, these declarations are more based on metaphysical convictions than empirical evidence. Ironically, those who currently consider religion a delusion often also deem Freud's psychoanalysis a pseudo-science. Fourth, the claim that the brain created God could easily be countered with the reversed claim that it was God who created the brain. If this reversed claim is correct, we do not project a human image onto heaven, but heaven shows us what human beings can and should be like.

However, a more serious case was made by the human geneticist Dean Hamer (2005). He theorized that if our sense of spirituality has a genetic basis, then those who rank higher in spirituality should share some genetic link that those who rank lower do not. He measured spirituality by using a "self-transcendence" scale developed by the psychologist Robert Cloninger, in order to quantify how "spiritual" someone is, based on the assumption that spirituality can be quantified by psychometric measurements. Hamer analyzed DNA and personality score data from over 1000 individuals, but limited his search for a "spiritual gene" to nine genes known to produce monoamines and then identified one particular gene, *VMAT2*, as showing a significant correlation with affinity for spirituality. When he analyzed this gene further, he discovered that those with the nucleic acid cytosine in one particular spot on the gene ranked high in spirituality, whereas those with the nucleic acid adenine in the same spot ranked lower. So, the question is: do we really have a discovery here?

First of all, gene *VMAT2* is basically a "pump" responsible for packaging a neurotransmitter for export during brain activity. In that specific sense, it is arguably an important gene, and its product may even be active when someone has "religious experiences," but that does not make this gene a "god gene." It is obvious that concepts of God do reside in our brains—they certainly do not reside in our toes—but that does not tell us where they ultimately come from. As an aside, one could even argue they do not

come from the brain but from the mind. This may not be mainstream thinking, but some very sophisticated scientific and philosophical thinkers—such as the Nobel laureate and neurobiologist Sir John Eccles, the philosopher of science and religion Richard Swinburne, and the philosopher of science Sir Karl Popper—are mind–body dualists who take the reality of the mental most seriously. Whether this does entail dualism is another issue.

Second, when it comes to religion, the cultural environment is particularly important, because religion is also a trait of our culture and personality. However, it has been proven to be hard to link individual genes to personalities, so it is very doubtful if we can possibly link them to religion. There are too many intervening steps involved—such as other genes, epigenetics, environmental effects on gene expression, cultural factors, and personal factors (see other chapters in this book)—to make such a simplistic link. Some traits can be hereditary without being genetic.

Third, Hamer (1994) has proved himself to be an expert in inventing genes—once it was a "gay gene," now a "god gene." Unfortunately for him, the field of behavioral genetics is littered with failed links between particular genes and behavioral traits. We have been bombarded with new genes: a gene for alcohol addiction, a gene for homosexuality, a gene for schizophrenia, a gene for altruism, and now even a gene for religion—the list could go on and on. Many of these were inventions that have never made it so far to becoming discoveries. It is also noteworthy to mention that Hamer rushed into print with his book without any peer review and without publishing his results in a credible and reputable scientific journal.

Fourth, even if it were true that we are genetically hard-wired for religion, what could this possibly mean? Clearly, we are not hard-wired for a particular religion; there are more than 7000 identified varieties. "Born a Catholic" does not mean always a Catholic. Plenty are the cases of people who, in the course of their lives, decided to become atheists or decided the opposite by leaving atheism behind. Even if some part of spirituality is wired in the brain, the forms and practices of religion are still cultural and can be passed from one person to another by learning or imitation and can be changed by further experiences.

Fifth, it is very doubtful whether all this genetic talk has actually anything to do with a Transcendent Being, God. Perhaps genetics can tell us something about mystical experiences, but the idea that people believe in God because of mystical experiences is foolish. One need not feel anything, let alone have a mystical experience, to believe in the existence of God. Arguably, most individuals who believe in God have never experienced God in a mystical way. Quite a few believe in God, or reject God, for purely intellectual reasons. Others simply have an intuitive awareness of God's existence. So, the label "god gene" is very deceiving, to say the least—which Hamer did acknowledge himself, though.

Sixth, a "feeling of transcendence" is not necessarily a religious experience, and if Hamer is right, it is in fact merely a biological one. The monoamines involved in the feeling of self-transcendence are the same monoamines that are jumbled by ecstasy, LSD, and other mind-altering drugs. If the feeling of transcendence is a biological experience rather than a religious experience, then studies performed on that experience only tell us something about biology, not religion—religion being an experience in terms of transcendence and the transcendent one, God.

Seventh, all of this prompts the question as to why Hamer wants to reduce religion and faith in God to something else, to something like spiritual experiences. The answer can perhaps be found in some underlying metaphysical presupposition—that biology can fully explain everything in life, including religious faith, beliefs, and experiences. This presupposition is based on the view that all reality can be reduced to a scientific explanation—a view we discussed earlier. True, if there is only material stuff in this universe, there is no longer room for spiritual reality—perhaps for spiritual experiences and sensations—but not for a reality behind and beyond those experiences. Hence, the "spiritual allele" of the "god gene" is not spiritual at all and can certainly not cause a religious experience. It may cause a natural sensation of self-transcendence that some have unwittingly interpreted as an encounter with the divine.

If you agree with these objections, religion can still stand tall next to science, unless…

THERE WOULD BE NO ROOM FOR RELIGION IF WE GO BY THE "HARD" FACTS

Many scientists believe that only science deals with what they call the "hard" facts, whereas religion does not and cannot. They come close to those who believe that, by giving a mighty kick to a stone, they have proved the reality of a "hard fact." When scientists proclaim "the facts tell us," they often think the discussion is closed, but "in fact" the discussion has just begun. Francis Crick (1990) was right on target when he said, "A theory that fits all the facts is bound to be wrong, as some of the facts will be wrong." Facts are not the "rock-solid" or "hard core" realities most people, including many scientists, think they are. So, let us find out what facts really are.

What is "out there" is not an assortment of rock-solid facts, but rather a collection of things, situations, and events; facts are merely our *interpretations* of the things and events we encounter around us—they are our way of making them *intelligible* for us. Things and events may be the "physical" parts of our world, perhaps even rock-solid,

but facts are "mental" creations—the interpretations of things and events in our minds. To use a distinction we discussed earlier, things and events are material entities, but facts are nonmaterial entities. Apparently, we need a clear-headed analysis first before we can go any further.

Let us start with what we usually agree upon when it comes to facts. Facts are supposed to be detached from time and space; they are true regardless of who you are and when and where you live; they appear as objective, absolute, and universal. On the other hand, once we start thinking and talking about them, facts seem to come back into space and time, because thinking requires *thoughts*, and talking requires *statements*. And that's what makes the situation so complicated, for now we end up with at least four rather disparate elements: events, thoughts, statements, and facts (White, 1970). How are they related, then?

Some people think that facts are the same as *events*, which the latter they regard as the "objective," "hard core" elements of this universe. The main reason for thinking this is that events seem the best candidates to offer us a rock-solid foundation for our facts. True, events do happen or do not happen; you can neglect them but not deny them. So by replacing facts with events, we might think we have found the strong objective foundation that we strive for. However, facts and events are concepts very different from each other. Unlike facts, events are dated, tied to space and time, whereas facts are detached from space and time, as we found out earlier. It is even considered a fact that certain events did not occur; it is a fact, for instance, that Darwin did not have a copy of Mendel's 1866 article in his collection. Apparently, a fact is not the same as an event; the best we can say is that a fact is a description of an event, but not the event itself.

This outcome has made some others claim that facts must be merely thoughts, then, existing only in our minds as something purely subjective. However, thoughts cannot be equated to facts. Thoughts can have some peculiar characteristics such as being imaginary, illogical, confused, time-consuming, and so on—whereas facts cannot. Facts, on the other hand, deal with what the events actually are, and not with what they might be. Facts are true, even if some people have never thought about them. Facts are always about something outside our thoughts and refer to something independent of our thinking. Therefore, a fact is not just a thought, but it may be the object of a thought.

A third solution might be that facts are identical to what people say about them—that is, the same as (true) statements. However, if that were the case, there would be as many facts as there are statements (for instance, facts would be different in English and Dutch). Obviously, facts have to be clearly distinguished from statements. Statements can be hypothetical, inaccurate, exaggerated, long-winding, and difficult to understand, and so on. Facts, on the other hand, cannot be any of these; a fact may be hard to accept, but never hard to understand; it is never hypothetical or half-true. There are even facts which everyone has forgotten or which were never expressed yet. Conclusion: a fact is not a statement, but it may be the content of a statement.

From this analysis follows that we are facing here an intricate situation: If facts are not events or thoughts or statements, what then are they? Facts actually feature as a focus point at the intersection of those three other elements: A fact is not an event but the description of an event, not a thought but the object of a thought, and not a statement but the content of a statement—and these can apply all at the same time. A more comprehensive definition of a fact could be like this: A fact is the description of an event, the object of a thought, and the content of a statement, all at once (Verschuuren, 1986). Facts are closely connected to these three other elements through the process of interpretation: facts are interpretations of events by means of thoughts and statements. It is through interpretation that thoughts and statements transform events into facts. Facts need events so they can be tested; they need thoughts so they can be understood; and they need statements so they can be discussed. Unlike things, events, and situations, facts are nonmaterial entities.

What this abstract discussion makes clear is that facts are always based on interpretations. If this is true, then there is no factual information without interpretation—and as a consequence, "no interpretation" would mean "no information." The more interpretation we inject, the more information we may provide, but also the more we need to prove. When I describe a certain event taking place in the sky as "Those are moving spots," I do express a fact, but it contains "empty" information, even though it is "safe" information. When I say, however, "Those are flying birds," my statement does convey additional information—and therefore I may need to come up with more evidence to support my claim. And when I say, "Those are migrating geese," I inflate my information even more, thus making my factual statement still more vulnerable.

Since facts are not objects like stones, we cannot bump into them. Therefore, there are no "hard core" facts, because facts cannot be touched, heard, or seen; events and things can, but facts cannot, as they are immaterial entities. Facts are about something "rock-solid," about something beyond our control, but they are not rock-solid themselves, since they have a man-made part, dependent on human interpretation. Facts are mental entities, so there is nothing physically solid about them—and yet, they are not purely mental creations either, because they are about something outside themselves, which is the final touchstone of that which a "fact" describes (otherwise they are not facts but imaginary thoughts or so).

Unlike animals, which only live in a world of things and events, human beings also live in a world of facts. By stating facts, they always claim much more than what they

"observe." In observation, one is both a passive "spectator" and an active "creator" at the same time. "Facts" transform "things" of the world into "objects" of knowledge; they change experiences into observations, thus enabling humans to see with their "mental eyes" what no physical eyes could ever see before. There would be no science without them.

HOW DO WE GET TO THE FACTS?

Getting to the facts is not as easy as opening your eyes. That is the reason why there is so much discussion about "the facts" in science. So, it should not really surprise us that the high-standard scientific journal *Nature* published a disturbing commentary claiming that in the area of preclinical research—which involves experiments done on rodents or cells in petri dishes, with the goal of identifying possible targets for new treatments in people—independent researchers doing the same experiment could not get the same results as reported in the scientific literature (Begley and Ellis, 2012). Over 10 years, Amgen researchers could reproduce the results from only 6 out of 53 landmark papers. And researchers at Bayer Healthcare reported that only in 20–25% of 67 projects analyzed the relevant published data were completely in line with their in-house findings.

Since we look at things as spectators, and then change them into facts as creators, we do not "have" observations—like we do have sensorial experiences—but we "make" observations. Philosophical giants such as Aristotle and Thomas Aquinas would put it this way: All we know about the world comes through our senses but this is then processed by the intellect that extracts from sensory experiences that which is intelligible. It is through facts that events become intelligible to us. Although we know the world through sensations or sense impressions, they are just the media that give us access to reality. The philosopher John Haldane (2011) put it well when he said, "One only knows about cats and dogs through sensations, but they are not themselves sensations, any more than the players in a televised football game are color patterns on a flat screen." Knowledge does rest on sensation and experiment, but this does not mean it is confined to it.

Yet, "reality" remains the ultimate foundation of all we know; so it should always be the ultimate touchstone of all our interpretations. But there is a problem here. Since we only know reality through (interpreted) facts, there is no direct way of comparing facts with reality. How could we ever compare "interpreted" facts with "hard core" reality if we have no access to reality other than through interpretation? How could we ever compare what we know with what we do not know (yet)? How could we ever step outside our knowledge and compare what we know with what we do not know yet? Think of this analogy: How would nearsighted individuals ever know that reality is not as blurred as they see it? Certainly not by comparing their own images with the "real" images, but perhaps by comparing their own images with the images received through different tools such as proper glasses.

The problem we have here is probably best expressed by Plato: "How would you search for what is unknown to you?" (*Meno*, 80d). Plato noticed a paradox here: We are in search of something "unknown"—otherwise we would not need to search anymore—and yet it must be "known" at the same time—otherwise we wouldn't know what to search for, or would not even know if we had found what we were searching for. That is the reason why we need hypothetical statements based on concepts, which work like "searchlights" that may help us illuminate what was in "darkness" before. That's how facts come about, in an interaction between thoughts, statements, and events. I borrowed the term "searchlight" from the physicist and philosopher Karl Popper (1979). As early as 1865, the biologist Claude Bernard (1957) had called a theory a "light" instead of an absolute authority.

Some have objected that the facts we know are part of our knowledge and therefore cannot be external to our knowledge; consequently, speaking in terms of anything "outside" our knowledge would be out of the question. In such a view, however, knowledge is conceived as though it were a box, allowing things only to be either inside or outside the box. On the contrary, knowledge is certainly not like a box. It may be best compared to a source of light, as Edmund Husserl (1970) sees it; if a light beam hits a certain thing that is in darkness, this thing will be in the light, and yet it would not be inside the source of light.

Concepts are the "searchlights" we need in order to search for new facts. Even such a simple process as generalizing from "some" to "many" cases, and ultimately to "all" similar cases—as is done in induction—is based on, well… *similarity*! However, similarity is not visible until we know already what these cases have in common. We need to identify first what is relevant to our problem, for similarity cannot be established until it has been identified in a word first, or actually in a concept. Before we can "notice" a carnivore, we need the "notion" of a carnivore to begin with. In other words, there is no recognition without cognition. Because concepts are the building blocks of thoughts and statements, scientists, for instance, are always in need of imaginative, bold ideas, outlined in what is called a hypothesis; it is this very hypothesis that makes them "see" the similarity that they were not able to see before. In science, all observations must be for or against some hypothesis or theory if they are to be of any service in science. As Charles Darwin put it in a letter to Henry Fawcett, "How odd it is that anyone should not see that all observation must be for or against some view if it is to be of any service!" (Darwin, 1861).

No wonder then that a camera, for example, cannot capture facts—all it can capture are things, situations, and events. Take a surveillance camera; it "observes" everything because it does not "know" what to observe. That is why cameras and other observational tools cannot replace scientists—they may be helpful to them but cannot replace them. The problem with pictures in general is that they do not show us facts until we give some interpretation to what is seen on the picture. The same with books: They provide lots of information for "bookworms," but to real worms they have only paper to offer. Facts carry a heavy man-made component.

Alas, hypotheses and theories just do not spontaneously emerge from observation. Biologists, for instance, were not able to see the similarity in building blocks between animals and plants until the concept of a "cell" had been established; neither could they see the similarity between leprosy and tuberculosis until the concept of "bacteria" had become available. Take this simple analogy: America did exist before it was "invented," but while still called the West Indies, it had not yet been "discovered."

IS THERE A WAY FOR SCIENCE AND RELIGION TO LIVE TOGETHER?

So far we have discussed one side of the coin: since facts carry a man-made component, they need to be tested and may have to be revised. But there is another side to the coin. Because of their man-made component, there can be various ways of looking at the same thing or event, which makes for various kinds of facts. Facts are always interpreted from a specific perspective and, since there are many more perspectives than what science tries to capture with its barometers, thermometers, and spectrometers, science does not give us the only window on the world; there are many other windows, views, vistas, aspects, perspectives, or whatever you wish to call them. Earlier, I discussed scientism as to its claim that science provides "the only source of genuine factual knowledge," but now we have even more reason to question what "genuine factual knowledge" really stands for.

Reality is like a jewel with many facets that can be looked at from various angles, from different viewpoints. Just like the "physical eye" sees colors in nature, so the "artistic eye" sees beauty in nature, the "rational eye" sees truths and untruths, the "moral eye" sees rights and wrongs, and the "religious eye" sees everything in relationship to God. All these "eyes" claim to be in search of reality, but each one "sees" a different aspect of it—and therefore sees different "facts." Let me use a more specific example. The "physical or biological eye" sees every beginning of new life as a fertilization process—a product of procreation. The "religious eye," on the other hand, sees it as a gift from Beyond—a product of creation. These two perspectives may be different, but certainly not contradictory, as they can both be true and qualify as "facts." A fertilized egg cell is the beginning of a human life, but it is not its origin. For the religious believer, the origin of every human life is God, for it is in God that we live, move, and have our being. To put it differently: *In* the beginning of one's life is God, but *at* the beginning of one's life is a fertilized egg cell. All of us may have very well come to this world *from* God, although we have come here *through* our parents. Something similar holds for the relationship between the Big Bang and Creation: the Big Bang may be about the beginning of the universe—that is, about what happened "*at* the beginning"—whereas Creation is about the origin of the universe, about what is "*in* the beginning." Creation is something "in the beginning," which made it possible for something to happen "at the beginning."

The fact that God is the origin of all human life may qualify as much as "fact" as the fact that human life comes from fertilized egg cells. Since all facts carry a man-made component, they can be seen from a specific perspective, yet supported by more or less evidence. Some facts—especially some scientific ones—come with an enormous baggage of background information and supporting observation techniques (without those, there would be no discovery of Higgs boson, for instance). And so do some religious facts according to religious believers. Undoubtedly, "bare" facts just do not exist. Religious facts are as "bare" as any other facts. The philosopher Ludwig Wittgenstein once worded it this way: "To believe in a God means to see that the facts of the world are not the end of the matter" (Wittgenstein, 1961). And Albert Einstein (1941) once said, "Science without religion is lame, religion without science is blind."

Instead of a "one-sided" outlook on events, the analysis I used in this chapter rather supports an "all-round" outlook. In Hamlet's words, there is so much more than dreamt of in your philosophy. As a matter of fact, reality may have different aspects and appearances to show, all of which can be equally real, valid, and objective. Without the appropriate conceptual and interpretational framework, many facts would escape notice. In order to obtain an idea of the many aspects of an event, we need to inspect it from different angles—that is, within different interpretational frameworks—otherwise we could miss out on some essential views. Thanks to human interpretation, reality has become a multifaceted phenomenon.

On the other hand, accepting that there are various interpretational frameworks does not mean that they can all be tested the same way—that is, the way things are tested in the empirical and experimental sciences, let alone in the natural sciences. Yet the question remains: is a religious outlook a valid outlook? I see no reason why not. Facts are

not material entities, so we found out, therefore they can never be "hard," "tangible," "audible," or the like—not even in science. We tend to *over*estimate the power of facts when it comes to science, whereas in religion, we tend to *under*estimate the power of facts. Put differently, as far as science is concerned, there is much more believing in what we know than many want to believe. And, vice-versa, in religion there may be much more knowing in what we believe than many seem to know.

But one could argue that all of this only makes for rather "negative" evidence in support of a religious outlook. Is there also "positive" evidence? Many philosophers and theologians have actually come up with positive evidence—which has sometimes been rejected by those with a preconceived idea of materialism or scientism. I would not go into those details but I will just raise a few rhetorical questions: could there be order in this world if there were no orderly Creator? Could there be scientific laws if there were no rational Lawgiver? Could nature be intelligible if it were not created by an intelligent Creator? Could there be moral laws if there were no moral Lawgiver? Could there be design in nature, if there were no intelligent Designer (let me stress that this is not equivalent to the so-called "intelligent design theory")?

The best and most rational answer to all these questions is a rather definite "No, there could *not*…"—unless one just wants to give up on rationality ahead of time. To put it positively, such answers work like powerful "pointers" to a Transcendent Being or Creator God as the best possible—and arguably only—rational explanation for the fact that this Universe does exist and is the way it is. The British physicist John Polkinghorne (1989) calls them "pointers to the divine as the only totally adequate ground of intelligibility." Rationality calls for an explanation—unless one decides to abandon rationality, but that is a position hard to defend on rational grounds. The answer that things just are the way they are is not a very satisfying response; our universe need not be the way it is, and it need not even exist. As the physicist Paul Davies (2000) said at one point, "There must be an unchanging rational ground in which the logical, orderly nature of the universe is rooted."

In other words, our rationality is based on the power of reason and reasoning. The mere *fact* that reason exists—including its order, its content, its principles, its rules, and its power—calls for an explanation. Reason tells us that only reasoned proofs and scientific evidence make our claims understandable, intelligible, justified, and true. Science itself arises from and rests upon these pillars—the certainty and strength of reason and its many principles and demands. If these were only based on individual, subjective, and personal sensations, we would lose the universal rational order that guides and evaluates all our thinking and all our scientific endeavors. We would end up with mere illusions or hallucinations. Thus the question remains what causes reason's order to exist. Leaving God out of the cosmos would reduce reason to a mere neural experience that leaves us only with the sensation of reason, without any further reality. We could even go as far as claiming that, without a Creator God, scientists would fundamentally lose their reason for trusting their own scientific reasoning. If God does exist, there is at least an explanation and foundation for the existence of reason and its order—which is so vital to science.

No doubt, the validity of any kind of religious perspective has been questioned repeatedly. Skeptics can be found anywhere. Not only do they attack the religious perspective, but also the scientific perspective. Skepticism makes for a very restrained view on the world—actually so restrained that absolute skeptics cannot even know whether they have a mind to doubt with. Skeptics turn things the wrong way. Granted, we often do need to eliminate errors to get to the truth, yet our ultimate goal is not to avoid errors, but to gain truth—to know rather than to know what we do not know. Skeptics, on the other hand, make it their final goal to avoid errors, in denial of the fact that eliminating errors is only a means to gaining truth about reality. Skeptics such as the philosopher David Hume question even the connection between cause and effect and consider it only a habit of our thinking as we become accustomed to see one thing constantly conjoined to another. It is hard to maintain, though, that scientific discoveries—whether it is pathways of metabolism, networks of neurons, the cellular process of protein synthesis, the cascade of coagulation, or the control mechanism of homeostasis—are merely based on our thinking habits.

Needless to say that a radical form of skepticism would not only undermine the very foundation of science, but also the adequacy and validity of any kind of religious outlook. As to whether this is an acceptable outcome is a decision I must leave up to you.

REFERENCES

Begley, C.G., Ellis, L.M., 29 March 2012. Drug development: raise standards for preclinical cancer research. Nature 483, 531–533.

Bernard, C., 1957. An Introduction to the Study of Experimental Medicine. Dover Publication, New York, p. 40.

Bullock, A., Trombley, S. (Eds.), 1999. The New Fontana Dictionary of Modern Thought. Harper Collins, London, p. 775.

Cloninger, C.R., 2004. Feeling Good: The Science of Well-being. Oxford University Press, New York.

Commoner, B., 1964. Roles of deoxyribonucleic acid in inheritance. Nature 202, 960–968.

Crick, F., 1990. What Mad Pursuit: A Personal View of Scientific Discovery. Basics Books, New York.

Davies, P., 2000. What happened before the big bang. In: Stannard, R. (Ed.), God for the 21st Century. Templeton Press, pp. 10–12.

Dawkins, R., 2008. The God Delusion, reprint ed. Mariner Books.
Einstein, A., 1941. In: Science, Philosophy and Religion, a Symposium (New York: The Conference on Science, Philosophy and Religion in Their Relation to the Democratic Way of Life).
Feser, E., 2014. Scholastic Metaphysics: A Contemporary Introduction. Editions Scholasticae.
Feyerabend, P., 1975. Against Method: Outline of an Anarchistic Theory of Knowledge. Verso Books, New York, p. viii.
Geertz, C., 1993. Religion as a cultural system. In: The Interpretation of Cultures. Fontana Press, pp. 87–125.
Haldane, J.B.S., 1928. Possible Worlds and Other Essays. Harper and Brothers, p. 209.
Haldane, J., 2011. Hume's destructive genius. First Things 218, 23–25.
Hamer, D., 1994. The Science of Desire: The Search for the Gay Gene and the Biology of Behavior. Simon and Schuster, New York.
Hamer, D., 2005. The God Gene: How Faith Is Hardwired into Our Genes. Anchor Books.
Hawking, S., 2002. In Interviews with Gregory Benford, "Leaping the Abyss: Stephen Hawking on Black Holes, Unified Field Theory and Marilyn Monroe. Reason, 4.02 (April): 29.
Husserl, E., 1970. The Crisis of European Sciences and Transcendental Phenomenology (C. David, Trans.). Northwestern University Press, Evanston, p. 6.
Letter to Henry Fawcett (18 Sep 1861). In Charles Darwin, Francis Darwin, Albert Charles Seward, More Letters of Charles Darwin (1903), vol. 1, 195.
Lewis, C.S., 1980. The Weight of Glory and Other Addresses, revised ed. Macmillan, New York, pp. 71–72.
Maslow, A.H., 1966. The Psychology of Science. HarperCollins, p. 15.
Nagel, T., 2012. Mind and Cosmos: Why the Materialist Neo-darwinian Conception of Nature Is Almost Certainly False. Oxford University Press.
Polkinghorne, J., 1989. Science and Creation. The Search for Understanding. Shambala, Boston, MA.
Popper, K.R., 1979. Objective Knowledge, revised ed. Clarendon Press, Oxford. Appendix 1: "The Bucket and the Searchlight – Two Theories of Knowledge.
Verschuuren, G.M.N., 1986. Investigating the Life Sciences. In: Foundations & Philosophy of Science and Technology Series. Pergamon Press, Oxford (Chapters 4 and 5).
White, A.R., 1970. Truth. Doubleday, Garden City, NY (Chapter 6).
Wittgenstein, 1961. Notebooks 1914–1916 translated by Gertrude Elizabeth Margaret Anscombe, first ed. Journal entry (8 July 1916), p. 74e

Chapter 41

Universal Humanity, Religious Particularity, and Scientific Reductionism

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One of the rapidly moving frontiers in university undergraduate education is Big History (Brown, 2007; Christian et al., 2014). The field of Big History now incorporates what was previously known as World History into a larger scheme: the evolutionary history of the universe. Like a series of Russian boxes, the rise of human civilization is fitted into a larger evolutionary box—biological adaptation for survival—and this in turn is placed within the still larger physical story of our cosmos. Within this telescoping framework the rise of human religious practices is thought to be the product of evolutionary adaptation, that is, religion has been naturally selected because it contributes to reproductive fitness.

However, I note that an explanatory gap has opened up, a gap between human reports of a transcendent divine reality and the attempt to provide an evolutionary explanation. A significant historically retrievable phenomenon has not been sufficiently accounted for by the big historians, namely, the Axial Breakthrough (Bellah, 2011, 2012; Jaspers, 1953; Voegelin, 1956–1987). By Axial Breakthrough, I refer to events shocking the human psyche that occurred in different parts of the world during the first millennium before the common era. After the rise of city-states and during the early stages of empire, a transcendental insight dawned on certain individuals in China, India, and the Middle East. This transcendental insight shed new light on the human condition in the recorded ruminations of Confucius, Lao Tzu, the Upanishadic Brahmans, the Buddha, Zoroaster, the Hebrew prophets, and Plato. Whether theists or nontheists, these thinkers cultivated belief in a transcendent moral order and transcendent ground for human reasoning that is trans-tribal and universal in scope. In some instances this breakthrough became the basis upon which whole cultures were constructed with local ethnic identities placed within a growing sense that there exists a single universal humanity. This ancient history gradually morphed over two-and-a-half millennia into contemporary beliefs in universal human dignity complemented with respect for ethnic and religious diversity.

The axial insight was partially mystical. As mystical, it was extra-linguistic while impacting linguistically formulated descriptions of it. These formulations were context-dependent, to be sure; yet each original context-dependent formulation contributed independently to the growth of diverse religious traditions. Thus, paradoxically, the mystical insight attests to a single ultimate reality while the diversity of religious traditions augurs our inescapable need for culture-specific symbol systems for apprehending the ultimate. We moderns live with both respect for cultural diversity and respect for a single universal humanity.

But we must ask: does reality match the appearance? Might axial insights and religious diversity be reducible to one and only one principle, namely, natural selection? Even though it appears that human seers have gained insight from a transcendental source such as God, is this a delusion fopped off on human consciousness by reproductive fitness? Even though the human mind wanders from thought to thought and poses questions about ultimate reality and ultimate meaning, can the mind be reduced to the brain's neuronal firings? Is human consciousness and transcendental awareness nothing but an epiphenomenon: ephemeral, delusional, and misleading?

Contemporary reductionists in three fields—sociobiology, neurophilosophy, and Big History—are looking for the underlying unity of human experience not in the transcendental claims of axial thinkers, but rather in the human brain that both axial and nonaxial persons share. "Current neuroscientific and psychological evidence [suggests a bioevolutionary explanation for nonlinguistic experience which accounts for] cross-cultural similarities. Rather than

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00041-7

indicating a common mystic object, such similarities may instead merely be products of the shared structure of the human brain," contends Jason Blum (Blum, 2014, p. 168). Such a reductionist position finds the unifying factor not in the mystical claim but rather in the brain that makes the claim.

Some nonreductionists are fighting back. Philosopher of science Thomas Nagel contends that reducing evolutionary theory to strictly physical and chemical causation prevents acknowledging what is empirically real, namely, living creatures with conscious self-understanding: "Physico-chemical reductionism in biology is the orthodox view, and any resistance to it is regarded as not only scientifically but politically incorrect" (Nagel, 2012, p. 5). Reducing life to its physico-chemical elements fails to explain it: "It is prima facie highly implausible that life as we know it is the result of a sequence of physical accidents together with the mechanism of natural selection" (Nagel, 2012, p. 6). So, internal to scientific method, Nagel urges a broadening to include distinctively human phenomena such as mind, consciousness, and selfhood: "The great advances in the physical and biological sciences were made possible by excluding the mind from the physical world. This has permitted a quantitative understanding of that world, expressed in timeless, mathematically formulated physical laws. But at some point it will be necessary to make a new start on a more comprehensive understanding that includes the mind" (Nagel, 2012, p. 8).

This is a step in the right direction, in my judgment. In addition to acknowledging the mere existence of consciousness, we need to take a further step and make room for the claims of consciousness. Included in the claims of human consciousness for three millennia now are claims of a transcendent ground to reality and of meaning to history. Such claims should be tested for their truth or falsity, not rejected a priori as epiphenomenal byproducts of physics and chemistry.

In what follows, I will point out the explanatory gap in three fields: neuroscience, sociobiology, and Big History. At stake is, first, the ontological status of human consciousness and, second, the integrity of religious claims made in various chapters of the human story. Axial claims interest us in particular, because they provide a theological grounding for the concept of a universal humanity that manifests itself in multiple culturally specific forms. More importantly, it is belief in a divinity who transcends the physical order which makes possible the meaningfulness of both natural and human history.

THE FIRST GAP: CONSCIOUSNESS IN THE CONTEXT OF NEUROSCIENCE AND NEUROPHILOSOPHY

One of the mantras repeatedly chanted by those who meditate on the advances in neuroscientific research is this: the brain-as-automatic-pilot has taken care of matters even before we become aware of it. Or, to say it another way: the brain is the hardware and the mind is the software. Or, to say it still another way, the mind is indistinguishable from the brain. "The mind…is the brain," writes philosopher Daniel Dennett (2006, p. 107). What this philosopher has done prematurely is to fill in a gap, an explanatory gap not yet bridged by actual laboratory researchers. What appears to be nonmaterial, our mind, is actually material after all. Thus says the materialist reductionist.

Back in the laboratory, brain researchers confront an explanatory gap between what we experience subjectively in consciousness and materialist attempts to explain this experience. "For no matter how deeply we probe into the physical structure of neurons and the chemical transactions which occur when they fire, no matter how much objective information we come to acquire, we still seem to be left with something that we cannot explain, namely, why and how such-and-such objective, physical changes, whatever they might be, generate so-and-so subjective feeling, or any subjective feeling at all," writes Michael Tye for the *Stanford Encyclopedia of Philosophy* (Tye, 2013). Third-person explanations simply cannot account for first-person experiences.

Despite the gap, some neuroscientists and many neurophilosophers rush in to fill it with materialist assumptions. They contend that objective explanations will eventually reduce subjective experience to that of a delusion. Dan Jones writes a virtual obituary for the human mind in the *New Scientist*: "Neuroscientists increasingly describe our behaviour as the result of a chain of cause and effect, in which one physical brain state or pattern of neural activity inexorably leads to the next, culminating in a particular action or decision. With little space for free choice in this chain of causation, the conscious, deliberating self seems to be a fiction" (Jones, 2011, p. 32). Physicist Stephen Hawking slams the lid shut on the consciousness casket: "recent experiments in neuroscience support the view that it is our physical brain, following the known laws of science, that determines our actions, and not some agency that exists outside those laws… It is hard to imagine how free will can operate if our behavior is determined by physical law, so it seems that we are no more than biological machines and that free will is just an illusion" (Hawking, 2010, p. 32).

On the one hand, laboratory brain researchers are more modest than the philosophers about their claims. Steven Rose, Director of the Brain and Behavior Research Group at the Open University in the United Kingdom, refrains from making claims about consciousness: "As neuroscientists we don't have anything very much useful to say about that particular Big C [Consciousness]…we would do better to keep silence" (Rose, 2005, p. 4). On the other hand, some such as French cognitive science researcher Stanislas Dehaene are attempting to turn "a philosophical mystery into a laboratory phenomenon" (Dehaene, 2014, p. 8).

Dehaene believes he can turn our first-person conscious experience of the self into a third-person quantitative analysis. "Even these higher-order meanings of consciousness are no longer inaccessible to experimentation. In our laboratories, we have learned to quantify what the 'I' feels and reports, both about the external environment and about itself" (Dehaene, 2014, p. 9). Does the translation of first-person accounts into third-person analysis eliminate the ontological status of first-person subjectivity? Will this come to mean that our first-person experience is but a delusion and that third-person analysis will take out a patent on reality?

Affirming this self-as-delusion position, neurophilosopher Thomas Metzinger pits the brain against subjectivity: "Subjective experience is a biological data format, a highly specific mode of presenting information about the world by letting it appear as if it were an Ego's knowledge. But, no such things as selves exist in this world" (Metzinger, 2009, p. 8). The self along with the mind can be reduced to biochemical activity in the brain; thereby, making our conscious sense of self-groundedness delusional. Almost like the Buddhist teaching of *anatta*, the teaching of today's neurophilosopher tells us to give up childish fairy tales such as consciousness, mind, and the subjective self.

Nonreductionists respond with cautious demure. While not denying the influence of the brain on the mind, objectors contend that the mind is not reducible to the brain. "Experience may arise from the physical, but it is not entailed by the physical. The moral of all this is that *you can't explain conscious experience on the cheap*," argues David Chalmers (Chalmers, 1997, p. 18, Chalmers' italics). In short, consciousness is reducible to neuronal firings according to the reductionists; but it is not reducible according to those who wish to protect the existence of consciousness, mind, and selfhood.

This leads philosopher Otfried Höffe to observe, "The actual insights of brain research offer in any event no dogmatic neuro-biologism according to which mind and consciousness *merely* emerge as natural events and according to which the social nature of humanity occurs exclusively on the basis of biological nature" (Höffe, 2010, p. 249).

Despite these, materialists press forward in public with their reductionist agenda. This elicits anxiety. Each of us feels at home in our subjectivity, in our consciousness. Subjectivity establishes who we are and where we are; it establishes who is the person experiencing the self and the world. Subjectivity instantiates us in being. So, for the neurophilosopher—ostensibly relying on the science of the brain—to explain our subjective first-person self-understanding in terms of something else elicits the fear that our personhood will be explained away. The third-person scientific perspective appears as a threat to our interior first-person self-understanding. This is an existential threat posed by an abstract discipline. We dare not underestimate the power of this existential threat to elicit anxiety.

Despite the rising anxiety, neurophilosophers continue to advance their reductionist agenda. Thomas Clark understands the existential anxiety his agenda elicits: "Involved here are fairly deep and emotional issues of human autonomy and specialness, especially the fear that if consciousness is nothing over and above physically instantiated function, then we lose our privileged status as rational agents riding above the flux of brute causality…If it turns out that subjectivity and the sense of self is merely function, then it becomes terrifying (for some) that no principled distinction may exist between us and a very clever robot" (Clark, 1997, p. 50).

But Clark has no intention of respecting this fear. He takes no prisoners. He presses forward with his task of finding a reductive explanation: "But of course we must not let such fears prejudice our initial conception of consciousness or restrict our investigation…As a scientific strategy for unifying knowledge, the reductionist impulse is hardly to be eschewed but rather to be encouraged…To reduce mental phenomena to functional processes via some plausibly evidenced identification is, after all, not to eliminate them, but simply to redescribe them from a third person perspective" (Clark, 1997, pp. 50–51). Clark supports the "*functional identity hypothesis*, which makes a strong claim…that subjectivity is constituted by those central representational processes which transform and enhance sensory information to the point where it normally dominates in the control of behaviour" (Clark, 1997, p. 52). In sum, Clark will not eliminate our first-person perspective; he will simply redescribe our first-person perspective in third-person terms. That is what science does, according to this philosopher.

Reductionists attempt to bridge the explanatory gap with promises drawn from their materialist presuppositions. Chalmers attempts to build a different kind of bridge. His bridge is made out of information. Because information is ubiquitously present in all physical reality, human consciousness based upon this physical substrate will continue to bear this information: "Information is truly fundamental…information is everywhere" (Chalmers, 1997, p. 27). The gap has now been closed, thinks Chalmers. A nonreductive yet physicalist explanation of conscious experience is just around the corner, he promises.

The reductionists want to defend their bridge from assault, so they fire back at Chalmers with heavy artillery. Because Chalmers sees a "gap," he is attacked by his reductionist critics on the grounds that he harbors a disguised Cartesian dualism: "The resulting naturalistic dualism Chalmers defends is Cartesian at its core, and despite his claim that such a position is entirely compatible with the scientific view of the world, dualisms have

fared badly as science proceeds to unify our conception of human kind in nature" (Clark, 1997, p. 48). Dennett describes the Chalmers position as "an imaginary dazzle in the eye of a Cartesian homunculus" (Dennett, 2006, p. 34). Materialist philosophers are at war with Cartesian substance dualism, and they are drafting neuroscience into their arsenal.

In sum, an explanatory gap exists between what brain researchers observe and the attempt to explain what they observe by appeal to material causation. To date, in the laboratory, human consciousness has defied reduction to physical or biochemical explanations. The explanatory gap remains. However, in contrast to neuroscientists who actually pursue the research, neurophilosophers try to fill in this gap with a priori assumptions derived from a materialist philosophy. This elicits anxiety; and anxiety keeps the discussion exciting. When pursuing empirical science along with sober reflection on that science, however, reductionist materialism gets in the way. It is my judgment that neuroscience needs to study human consciousness toward the end of explaining it, not explaining it away.

This is the point made by Nagel: a scientific method which will allow only physical and chemical explanations just may preclude itself from understanding what lies right before our eyes, namely, consciousness, mind, and self: "If the mental is not itself merely physical, it cannot be fully explained by physical science" (Nagel, 2012, p. 14). Perhaps scientific methodology should consider self-broadening. Without such broadening, we will lose the ontological status of consciousness, mind, and selfhood. Along with this loss, we will also lose the claims made by conscious persons, including claims about transcendent reality.

We have just defined the gap between first-person experience and third-person explanation, between neuroscience and neurophilosophy. The field of sociobiology opens up a second gap, a gap between genetic determinism and religious consciousness. Here we will see the same play performed on a different stage. In sociobiology what gets reduced is religious consciousness and, thereby, religious claims.

THE SECOND GAP: RELIGION IN THE CONTEXT OF SOCIOBIOLOGY'S ACCOUNT OF EVOLUTION

Religion evolved as a cultural institution to serve the reproductive fitness of *Homo sapiens.* Because religious societies make more babies that grow to reproductive age, religion was selected for, and became a trait of, the human race. How do we know this? It is a deduction from a premise, namely, that all of culture has evolved to serve reproductive fitness. So goes the argument in fields, such as sociobiology and evolutionary psychology which—regardless of their credibility as scientific research programs—are sponsored by well-respected members of the international scientific community. Therefore, we should accept at least at the level of assumption that religion, like all cultural forms, is a product of biological evolution; and religion can best be explained by appeal to evolution for its explanation.

The key that unlocks the explanatory power of evolution, according to sociobiologists, is DNA replication. Oxford's Richard Dawkins exclaims, "we are…robot-vehicles blindly programmed to preserve the selfish molecules known as genes." The genes are in the driver's seat; and human organisms like all organisms get taken for an evolutionary ride. We are "manipulated to ensure the survival of [our] genes" (Dawkins, 2006, p. x). Similarly, the American founder of the field of sociobiology, Edward O. Wilson, makes the same point this way: "the individual organism is only the vehicle [of genes], part of an elaborate device to preserve and spread them…The organism is only DNA's way of making more DNA" (Wilson, 1975, p. 3).

Now, back to our focus: the religious claims of human consciousness. Wilson asks, what is the origin of religion? "At some point in Late Paleolithic times, people began to reflect on their own mortality," wondering what happened to their relatives after death. "The departed still lived, and regularly rejoined the living—in dreams" (Wilson, 2012, p. 264). Dreams and visions and hallucinations were mistakenly thought to be revelatory; so religious authority and doctrines grew. Creation myths developed, assuring "the believers that they are paramount in the sight of God. Religious faith offers the psychological security that uniquely comes from belonging to a group" (Wilson, 2012, p. 266). "Perhaps it [shared belief in God] is no more than a tribe united by a creation myth. If the latter, religious faith is better interpreted as an unseen trap unavoidable during the biological history of our species…Humankind deserves better" (Wilson, 2012, p. 267). Evidently, Wilson believes religion was an evolutionary mistake. We deserve better. What might be better? Science, of course.

Before looking for what is better than religion, let us remind ourselves of just how this purported origin determines the essence of religion: "Humanity lives in a largely mythic, spirit-haunted world. We owe that to our early history…To explain the mysteries of their existence, they [humans at an earlier stage of evolution] believed in the superior beings otherwise like themselves, the divine ones who built not just stone tools and shelters but the whole universe…The *only* way our forebears could manage to explain existence itself was a creation myth. And every creation myth, without exception, affirmed the superiority of the tribe that invented it over all other tribes. That much assumed, every religious believer saw himself as a chosen person. [This view was] conceived in ignorance of most of the real world" (Wilson, 2012, p. 291). Our religious ancestors were ignorant and produced creation myths out of

their ignorance; but today Wilson will produce creation stories based upon knowledge—scientific knowledge—which will dispel this ignorance.

At work here is the assumption that yesterday's origin determines today's essence: "True to their biological origins, they [religions] passionately encourage altruism within their membership, and systematically extend it to outsiders, albeit usually, with an additional aim of proselytization. Commitment to a particular faith is by definition religious bigotry" (Wilson, 2012, p. 292). To be religious is to be bigoted.

When it comes to the claims enunciated by axial mystics regarding a transcendent order of justice, a universal humanity, and a life beyond this one, Wilson will hear none of it. It is with considerable passion that Wilson trumpets that we should "repudiate, respectfully, the claims of those in power who say they speak for God, are a special representative of God, or have exclusive knowledge of God's divine will. Included among these purveyors of theological narcissism are would-be prophets, the founders of religious cults, impassioned evangelical ministers, ayatollahs, imams of the grand mosques, chief rabbis, Rosh yeshivas, the Dalai Lama, and the pope" (Wilson, 2012, p. 293). In place of these spokespersons for God, Wilson will place himself as the spokesperson for evolution and a naturalistic ethic of universal altruism. Wilson's tribe of scientists must defeat these religious tribes in order to establish a supratribal worldview based on science. The scientific worldview will save humanity, save us most of all from the degrading forces of religious bigotry.

In sum, organized religion is an expression of tribalism organized eusocially around creation myths that maintain tribal identity. By retelling ancient creation myths in terms of biological evolution, Wilson is in effect trying to organize a new tribe of those in-the-know to engage in battle against anachronistic religious tribes who still live in ignorance. Intertribal war goes on. The new war will be between the tribe of scientists, on the one side, and their enemies, a federation of bigoted religious believers, on the other side. I take this to be the self-understanding of the sociobiologist.

Let's look again. In the case of sociobiology, there is more than mere scientific observation going on. Providing a scientific definition of religion with an accompanying evolutionary explanation is not all that is at stake. Despite the alleged fact that religion has been selected by natural selection, E.O. Wilson plans to deselect religion by his theory of evolution. Even if evolutionary biology in the past selected religion; Wilson plans to take the action in the future that will deselect it in favor of something better, namely, science. The future of our evolution will now be guided by the conscious scientist to select for science and deselect for religion.

The framework within which E.O. Wilson approaches the relationship between science and religion is what Ian Barbour identifies as the conflict model (Barbour, 1990, pp. 3–30). Another way to describe the position Wilson takes is to see it as scientific imperialism (Peters, 2003, p. 17). According to this model, science and religion are at war with one another, each trying to defeat the other and win by establishing a dominant worldview. The victory in Wilson's case need not be total. Wilson's military objective is to subjugate religion by providing an explanation for religion within bioevolutionary terms. What characterizes scientific imperialism is its goal of conquering the territory formally possessed by theology and claiming it as its own. For Wilson, biologists can better explain religion than theologians can. Therefore, theologians are out of a job, replaced by biologians.

The methodological point here ought not to be missed. By providing an evolutionary explanation for the phenomenon of religion, the sociobiologist need not attend to the truth or falsity of religious claims. Whatever claims about transcendent reality have been voiced by religious spokespersons can be reduced to physical and biological factors operative in evolution. This reduction applies to every human phenomenon except one: Wilson's own science. Natural selection should select Wilson's science for our evolutionary future; and in order to make this happen Wilson's science will have to win over religion in the struggle for existence. What looks like a mere scientific theory has become a formidable species fighting for the extinction of human religion.

The image evoked by Wilson is the biblical Battle of Armageddon, in which the forces of light defeat the forces of darkness: "The Armageddon in the conflict between science and religion…began in earnest during the late twentieth century. It is the attempt by scientists to explain religion to its foundations…At its source, the struggle is not between people but between worldviews" (Wilson, 2012, p. 255). Wilson's worldview represents the light; whereas a religious worldview represents the darkness to be conquered.

Religion deserves to lose, because it spreads darkness and ignorance "Why…is it wise openly to question the myths and gods of organized religions? because they are stultifying and divisive…Because they encourage ignorance, distract people from recognizing problems of the real world" (Wilson, 2012, p. 292).

In order to overcome the divisive darkness and ignorance plaguing our society due to organized religion, rational and scientific individuals should press forward toward a secularized worldview. One of the most potent weapons "is the increasingly detailed scientific reconstruction of religious belief as an evolutionary biological product. When placed in opposition to creation myths and their theological excesses, the reconstruction is increasingly persuasive to any even slightly open mind" (Wilson, 2012, p. 293). Note how evolutionary theory has become something much more than a mere scientific explanation for

observable phenomena; it has become a weapon in Wilson's war against religion.

Should the war end in favor of the army of scientific imperialists, then an elite of benevolent secular dictators would teach their ignorant religious subjects the truth about the real world. Defeated religious warriors should celebrate their surrender and welcome this enlightenment: "Science…is the wellspring of all the knowledge we have of the real world that can be tested and fitted to preexisting knowledge… It is not just another way of knowing as often claimed, making it coequal with religious faith. The conflict between scientific knowledge and the teachings of organized religions is irreconcilable" (Wilson, 2012, p. 295).

At this point we need to distinguish between science and scientism. "*Scientism*," according to David Ray Griffin, is "the belief that the scientific method…is the only way to discover truth" (Griffin, 2000, p. 10). Francisco J. Ayala represents science as science apart from scientism when he affirms that "science is a way of knowing, but it is not the only way" (Ayala, 2007, p. 177). But for Wilson, in contrast to Ayala, science is the *only way*. "Science…is the wellspring of all the knowledge," pens Wilson, assuming that his own ranting counts as scientific knowledge. What is happening is that the good name of science is being invoked to bless a secular ideology, a virtual secular counterpart to religion. "Whenever science becomes scientism, science not only ceases to be science and changes into religion, but becomes an intolerant danger for liberal societies," Markus Mühling warns us (Mühling, 2014, p. 27). What we have in Wilson's sociobiology is not laboratory research tendering a theory to explain human history. Rather, it is an ideology aimed at justifying scientific imperialism. No one need fear authentic science. But Wilson's scientism looks like the very religion against which he is going to war.

THE THIRD GAP: BIG HISTORY AS THE COMPREHENSIVE CONTEXT

Let's add a third gap: the gap opened up by Big History between natural meaninglessness and historical meaningfulness. Big Historians view both natural and human history through reductionist lenses, blinding them to historical moments where transcendent meaning engages history.

The Big History movement in higher education incorporates the history of human civilizations into a larger story of nature where evolution in both its biological and cosmic form is the protagonist. According to the International Big History Association, Big History "seeks to understand the integrated history of the Cosmos, Earth, Life, and Humanity, using the best available empirical evidence and scholarly methods" (IBHA, 2014). Or, Big History is "the attempt to construct a united account of the past at all scales from those of human history to those of cosmology; the modern scientific equivalent of traditional origin stories" (Christian et al., 2014, p. 307). Or, according to the late Robert Bellah, history and prehistory can be described together: "History goes all the way back and any distinction between history and prehistory is arbitrary. That means that biological history—that is, evolution—is part of the human story all the way through" (Bellah, 2011, p. ix). The concept of evolution unites what were previously separate: natural history and human history.

Building on a Darwinian foundation, big historians are constructing a metanarrative to explain everything from the Big Bang to our own era on Earth. "Fifty years ago, the suggestion that Darwinism might make some contribution to philosophical understanding would have been greeted somewhat like a bad smell at a vicarage tea party," writes Michael Ruse. But today evolution's explanatory province has expanded to include "both the theory of knowledge (epistemology) and the theory of morality (ethics)" (Ruse, 2013, p. 28). For today's big historians, evolutionary philosophy now explains the entire history of the cosmos inclusive of human history, knowledge, and ethics. The concept of evolution is no longer limited to explaining speciation as it was for its founder, Charles Darwin. Now, it allegedly explains everything.

Like the neuroscientists, big historians must confront an explanatory gap. Up until this point, we have lived with two histories: natural history and human history. Classically, we know that natural history is without *telos*, purpose, or direction, thereby making it meaningless or valueless. In contrast, because human history includes the story of human subjectivity, the meaning of history becomes central to every endeavor to reconstruct the past. In short, we confront a gap between prehuman meaninglessness and human meaningfulness. The big historian's self-assignment is to put the two together. Just what will bridge the two? The big historian's answer: evolution. The natural history of the evolution of species on planet Earth will become the bridge over the gap between physical history prior to the arrival of human consciousness and human history, which records the adventures of human consciousness.

Will the conflation of natural history with human history have meaning? With the question of history's meaning in mind, we must pose a postmodern question: who's history is Big History? A paradoxical metanarrative among the deconstructionist postmodernists is that there is no metanarrative. There is no value-neutral or meaning-neutral stance, say these postmodernists (Lyotard, 1992, p. 19). Therefore, every metanarrative is perspectival whether its projectors recognize their perspective or not. Every metanarrative comes from some place and reflects somebody's social location, tradition, and vested interests. Every metanarrative is the product of somebody's subjective consciousness.

Big History is a metanarrative. It must be if it is to be big. It must be if it is to be history. Now, I approve of such a metanarrative. I do not belong to the skeptical school of deconstructionist postmodernism. Yet, the question remains: who's subjective perspective determines the meaning of Big History? What is the vested interest of the big historian? What might be the ideology through which the big historian will interpret the cosmic and human past?

Our culture, like every coherent and enduring culture, requires a metanarrative if it is to enjoy meaning and if it is to understand itself. Yet, if big historians adopt a strictly scientific perspective without incorporating the subjective dimensions of our distinctively human reality, it will be difficult to acknowledge the perspective of the big historian and even more difficult to appreciate the history of human subjectivity which makes historical meaning possible. If big historians incorporate the materialism and reductionism we see in neurophilosophy and sociobiology into their method, then certain voices will be silenced: the voices of consciousness, mind, self, and God.

Allegedly, everything belonging to the human phenomenon, according to the big historian, can be reduced to one principle: the force of evolutionary development. "The scope of the concept of evolution" is expanding "to include cosmic and cultural history," according to big historian Ken Gilbert (Gilbert, 2014, p. 135). Our human civilization today is the product of "an evolutionary force in nature analogous to the force of gravity" (Gilbert, 2014, p. 142). This is curious. Physicists know four forces: gravity, electromagnetism, the strong nuclear force, and the weak nuclear force. Biology adds no forces to these four. Evolution obeys the same four forces that nonliving physical entities obey. But Gilbert invents a new force—*an evolutionary force*—found in biology; and then he retroactively moves it back from biological evolution so that now it applies to cosmic evolution. And he moves it forward to apply to human cultural evolution. All things prehuman and human now find one convenient explanation: evolution. Gilbert's enthusiasm for evolution might be tolerable; but his rewriting the science textbooks in order to ground all that happens in Big History in an imaginary evolutionary force is nothing but ideology. Because it is dressed in scientific apparel, the otherwise nude ideology is covered over.

When the scientific gaze turns science into scientism—that is, when science becomes a worldview or ideology—then, the door opens to nihilism. Wilson finds in his scientism a thrilling ideology; but most laboratory scientists rebel at the thought that their work might become co-opted by an implicitly nihilistic ideology. "By *scientism* I mean the absurdly reductionist belief that all truth can be learned and all reality described through science (never defined) and only through science," writes geochemist Rustum Roy (Roy, 2005, p. 836). The nihilism built into scientism finds a dramatic voice in biologist Jacques Monod: "The ancient covenant is in pieces: man at last knows that he is alone in the unfeeling immensity of the universe, out of which he has emerged only by chance. Neither his destiny nor his duty have been written down" (Monod, 1972, p. 167). My concern here is that if Big History becomes the metanarrative of scientism, the reductionist perspective may obliterate a decisive chapter in the cultural story, namely, the axial breakthrough to transcendence and the meaningfulness of history.

Nihilism is inescapable when one eliminates first-person human consciousness from what counts as a scientific explanation. This is because all meaning—including the meaning of nature—is the product of human consciousness. Once human consciousness has been reduced to neuronal firings or reproductive fitness, all meaning disappears from the objective domain. To have meaning, one must afford ontological respect to the consciousness of human selves.

What we have done so far is put together the fields of neurophilosophy, sociobiology, and Big History. In these three cases, we find an attempt to explain—actually, explain away—the phenomenon of religious consciousness in terms of the larger bioevolutionary development of life on Earth. The emergence of human awareness of transcendent reality should, in principle, be reducible to the physical and chemical processes which constitute human brain function. So the reductionist argument goes. Should this argument remain without challenge?

Referencing the axial age with open eyes itself constitutes a challenge of sorts. The axial age precipitated a deep enhancement in human subjectivity, the very subjectivity which eventually made the writing of meaningful history possible. Therefore, any historical account which does not include the history of subjectivity as its object would not be genuine history; it would amount to a mere agglomeration of natural facts strung together. In addition, any history which does not acknowledge the meaning structure presumed by the historian telling the historical story would disguise his or her subjective perspective; and this would imply, de facto, a form of nihilism. In short, I recommend that big historians pause to assess the impact and import of the axial age on the very subjectivity that makes possible their reconstruction of natural and human history. But to do so, they may have to forsake their scientism, materialism, and reductionism.

FROM BEYOND NATURE AND HISTORY: THE AXIAL BREAKTHROUGH

"Religion is the vision of something which stands beyond, behind, and within, the passing flux of immediate things; something which is real, and yet waiting to be realised; something which is a remote possibility, and yet the greatest of present facts; something that gives meaning to all that

passes, and yet eludes apprehension; something whose possession is the final good, and yet is beyond all reach; something which is the ultimate ideal, and the hopeless quest" (Whitehead, 1925, p. 238). This is what religion is, according to Alfred North Whitehead. What he is describing could not have come into human consciousness if the axial breakthrough were not an earlier chapter in our human story.

Among contemporary philosophers of religion representing a variety of religious traditions, the axial insight persists. "All the great world faiths affirm, in their different ways, the indescribable nature of the ultimate," trumpets John Hick (Hick, 2010, p. 164). Hindus especially feel a mission to maintain and recast this axial insight: "Truth may be one, but we will need many paths to it—with diversity, tolerance, and dialogue—if we seek to grasp its entirety…This is the real idolatry—taking one's immediate perspectival knowledge for the whole" (Kasturi et al., 2014, p. 37).

The label for this view is *pluralism*: "Polycentric pluralism would hold that the religions are completely distinct and unrelated, each worshipping or otherwise responding to its own Ultimate, and with its own path to its own expected end" (Hick, 2010, p. 156). Pluralists claim that culturally specific religious language points to an ineffable transcendent reality which is eternal and universal; and this ground of all being conditions human existence even while it itself remains unconditioned. This is one of the many claims lifted up by contemporary human consciousness, a claim a priori dismissed by a method that seeks to reduce the very consciousness that raises this claim to physical and chemical processes.

Even though I speak frequently of the axial insight as if it marked a eureka moment, that insight might be a response to an external stimulus. Instead of a human discovery of the transcendent, it might have been the transcendent which initiated the encounter. It appears that human consciousness was shocked during the axial period, shocked by a reality beyond daily understanding or comprehension.

The originator of the term, *axial age*, was German philosopher of history, Karl Jaspers. "What is new about this age, in all three areas of the world [China, India, Eurasia], is that man becomes conscious of Being as a whole, of himself and his limitations. He experiences the terror of the world and his own powerlessness. He asks radical questions. Face to face with the void he strives for liberation and redemption. By conscious recognizing his limits he sets himself the highest goals. He experiences absoluteness in the depths of selfhood and in the lucidity of transcendence" (Jaspers, 1953, p. 2). Human consciousness now asks: is this world all there is? Is there more? Is there an ultimate reality which transcends this one? (Eliade, 1957, p. 64).

Might these questions have been a response to a stimulus, the entrance of the transcend into the mundane? Or, to ask it another way: might the axial insight be the human response to a revelation of the ineffable God? Certainly a Muslim 1000 years after the axial age would answer in the affirmative" "God! There is no God but Him, Living, Self-sufficient. Slumber cannot seize Him, nor sleep. To Him belongs all in the heavens and on the earth…His Throne extends over the heavens and earth, which He preserves untiringly" (Qur'an, 2:255).

With the axial insight, critical philosophy is born right along with its twin, belief in a transcendent moral order "Man becomes conscious of Being as a whole, of himself and his powerlessness. He asks radical questions. Face to face with the void he strives for liberation and redemption. By consciously recognizing his limits he sets himself the highest goals. He experiences absoluteness in the depths of selfhood and in the lucidity of transcendence. In this age were born the fundamental categories within which we still think today" (Jaspers, 1953, p. 2). It takes a philosophical apprehension of a transcendent reality in order, eventually, to ground what we moderns deem to be universal: justice, equality, dignity, rights, and planetary responsibility. Only when grasped by what is real can we let go of our vested interests or myopic tribalism to embrace universal values which transcend what is local, parochial, or private. We are in a position to see the relationship of the part to the whole: "In *speculative thought* he [the axial seer] lifts himself up towards Being itself, which is apprehended without duality in the disappearance of subject and object, in the coincidence of opposites. That which is experienced in the loftiest flights of the spirit is a coming-to-oneself within Being, or as *unio mystica* as becoming one with the Godhead" (Jaspers, 1953, p. 3).

For ancient Israel, God was responsible for this transcendent moral order, which took the form of the Torah or divine Law. Our moral obligations became identified with ultimate reality, with God, according to biblical scholar Walter Brueggemann: "God is *an agent of judgment and restoration…ultimate accountability* and such *emergence of relational (covenantal) good* in biblical tradition are credited to an active, willful agency who is known by name, whose name attests to the personal, relational dimension of ultimate reality" (Brueggemann, 2014, p. 49).

Now, to be clear, I am not suggesting that human morality was given birth for the first time by an axial mother. More prosaic evolutionary explanations of a much earlier rise of moral awareness suffice. It seems obvious that as human intelligence increased, so did the intellectual power to discriminate between better and worse future scenarios. It is easy to surmise how standards such as better versus worse or right versus wrong would arise early in the *H. sapiens* story. And such moral standards were no doubt adaptive. Darwin himself predicted this: "Any animal whatever, endowed with well-marked social instincts…would inevitably acquire a moral sense or conscience" (Darwin, 1874, p. 98). Richard Joyce dubs this *native moralism,* the position that "morally

assessing aspects of one's environment (and oneself) enhanced the reproductive fitness of our ancestors" (Joyce, 2013, p. 464).

The leap in being taking place during the axial period builds on this more primitive moral notion. Because of the transcendental leap, objective and universal principles could emerge. Over against the oneness of divinity the entire world could now be seen as a unity, as an ecumenic or comprehensive unity. This new insight revealed an ideal, namely, the universal human race. Even though no one could empirically demonstrate that a single universal human race exists, this idea presented itself to human consciousness as a transcendent ideal and as an ethical standard for moral deliberation.

I must stress how important in the human story was the birth of the concept of a *Universal Humanum*: "The understanding of a universal humanity originates in the experience of transcendence; and the ineffable kinship of under God revealed in the experience can immanently be expressed only through a myth of descent from a common mother or father" (Voegelin, 3:107). It took a mystical experience with a heavenly reality for us on Earth to realize our extratribal unity, our *Universal Humanum*. We do not experience the *Universal Humanum* on a daily basis, yet it has become the moral order of the universe as we moderns view it. For this we can thank the axial insight.

On the one hand, axial seers were grasped by the transcendent, sometimes thought of in divine terms. On the other hand, by measuring the empirical world of daily life over against the envisioned ideal, our ancestors could construct ethical norms that reflected a universal and timeless moral order: "The theoretical breakthrough in each axial case led to the possibility of universal ethics, the reassertion of fundamental human equality, and the necessity of respect for all humans, indeed for all sentient beings. And yet in each case these assertions came out of living communities whose religious practices defined who they were and whose stories were essential to their identities" (Bellah, 2011, p. 606).

The axial age made the modern age possible. It would be curious if today's scientists would look back and eliminate the axial insight from our remembered and precedent-setting history. This would be like a tree branch severing its relationship to its trunk and roots.

It is curious that in his haste to explain the phenomenon of religion in biological terms that Wilson limits his description to tribalism and bigotry. That is all religion is: tribalism and bigotry. Wilson feels he can renounce tribalism and bigotry because he himself takes a universalistic and unprejudiced perspective. But, he fails to footnote axial religion. Like a scientific paper, which neglects to give credit to previous research, Wilson neglects to give credit to the very religious insight that makes possible his criticism of tribalism and bigotry.

In part, today's axial thinking is constructive, perhaps reconstructive. The material out of which we construct our picture of the axial era is the surviving symbols, liturgies, and belief systems of the living religious traditions. Some of our religious traditions bear into the modern world the axial insight; and they continue to inspire segments of our emerging global society with high ideals and hope for the future. The emerging planetary society will be constructed out of a plurality of religious symbol systems, each of which individually points to a universal transcendent reality and the accompanying hint that we must think ethically in terms of a single universal human race.

CONCLUSION

Because today's Christian theologians draw primarily from Scripture and secondarily from ancient Athenian philosophy, they cannot help but say "thank you" to the ancient axial prophets. By synthesizing an axial notion of a transcendent creator God with a big history interpreted in part through evolutionary lenses, today's theistic evolutionists can find meaning in both natural and human history. The Jesuit Titan of 20th-century theology, Karl Rahner, saw it this way: "Is a continuous development of the cosmos from its simplest and most original components right up to its present differentiation and complexity, the realm of living being included, acceptable to Christian faith in such a way that it can leave this whole evolution to natural science as a thesis or hypothesis, and then, at most, afterwards include this evolution in a Christian conception of the world? Our answer is yes" (Rahner, 1988, XXI: 38). The 21st-century systematic theologian Elizabeth Johnson, sees it the same way: "The mystery of the living God, utterly transcendent, is also the creative power who dwells at the heart of the world sustaining every moment of its evolution" (Johnson, 2007, p.188).

Evolutionary theory need not a priori eliminate from its purview the axial chapter in the human story. Nor does evolutionary theory need to eliminate at the level of assumption the existence of God or the human experience with transcendent reality. Evolutionary theory can be compatible with theism as well as other forms of religious belief. The key is this: evolutionary theory should stick to its original purpose, namely, to explain speciation in biology. Charles Darwin titled his principal book of 1859, *The Origin of Species,* because he had discovered how variation in inheritance and natural selection could explain speciation. This theory did not purport to explain other things such as the origin of life, the origin of the universe, or the origin of reductionist materialism. Claims made by axial prophets to have experienced a shock in their consciousness due to the presence of the divine are simply not the subject matter of Darwinian evolution. For the big historian to subordinate everything happening in big

history to a fictional "evolutionary force" is to promulgate an ideology of scientism. Evolutionary theory without scientism can still function as a fertile research program without interfering with other truths in the human psyche.

"The message has always been twofold," writes Francisco J. Ayala, "(1) evolution is good science and (2) there need not be contradiction between evolution and religious beliefs" (Ayala, 2007, p. 5). Ayala offers our conclusion: "Yes, one can believe in both evolution and God…evolution is not the enemy of religion but, rather, its friend" (Ayala, 2010, pp. 82–83).

REFERENCES

Ayala, F.J., 2007. Darwin's Gift to Science and Religion. Joseph Henry Press, Washington.

Ayala, F.J., 2010. Am I a Monkey? Six Big Questions about Evolution. Johns Hopkins University Press, Baltimore.

Barbour, I.G., 1990. Religion in an Age of Science. Harper, San Francisco.

Bellah, R.N., 2011. Religion in Human Evolution: From the Paleolithic to the Axial Age. Harvard University Press, Cambridge MA.

Bellah, R.N. (Ed.), 2012. The Axial Age and its Consequences. Harvard University Press, Cambridge MA.

Blum, J.N., March 2014. The science of consciousness and mystical experience: an argument for radical empiricism. Journal of the American Academy of Religion 82 (1), 150–173.

Brown, C.S., 2007. Big History from the Big Bang to the Present. The New Press, New York.

Brueggemann, W., 2014. Embracing and/or refusing god-talk. Tikkun 29 (3), 49–50 (Summer).

Chalmers, D.J., 1997. The hard problem: facing up to the problem of consciousness. In: Shear, J. (Ed.), Explaining Consciousness–the Hard Problem. MIT Press, Cambridge MA, pp. 9–30.

Christian, D., Brown, C.S., Benjamin, C., 2014. Big History between Nothing and Everything. McGraw-Hill, New York.

Clark, T.W., 1997. Function and phenomenology: closing the explanatory gap. In: Shear, J. (Ed.), Explaining Consciousness–the Hard Problem. MIT Press, Cambridge MA, pp. 45–60.

Dawkins, R., 2006. The Selfish Gene. Oxford University Press, 30th Anniversary Edition, Oxford and New York.

Dehaene, S., 2014. Consciousness and the Brain: Deciphering How the Brain Codes Our Thought. Viking, New York.

Darwin, C., 1874. The Descent of Man, and Selection in Relation to Sex, second ed. John Murray, London.

Dennett, D., 2006. Breaking the Spell. Viking, New York.

Eliade, M., 1957. The Sacred and the Profane: The Significance of Religious Myth, Symbolism, and Ritual within Life and Culture. Harcourt, Brace, and World, New York.

Gilbert, K., 2014. The universal breakthroughs of big history: developing a unified theory. In: Grinin, L., Baker, D., Quaedackers, E. (Eds.), Teaching and Researching Big History: Exploring a New Scholarly Field. Uchitel Publishing House, Volgograd, Russia, pp. 112–146.

Griffin, D.R., 2000. Religion and Scientific Naturalism: Overcoming the Conflicts. SUNY, Albany NY.

Hawking, S., Mlodinow, L., 2010. The Grand Design. Bantam Books, New York.

Hick, J., 2010. The New Frontier of Religion and Science: Religious Experience, Neuroscience and the Transcendent. Macmillan, Palgrave, New York.

Höffe, O., 2010. Can Virtue Make Us Happy? In: Douglas, R., McGauhey, Aaron Bunch (Eds.) Northwestern University Press, Evanston IL.

International Big History Association (IBHA), 2014. http://www.ibhanet.org/.

Jaspers, K., 1953. The Origin and Goal of History. Routledge, New York.

Johnson, E.A., 2007. Quest for the Living God: Mapping Frontiers in the Theology of God. Continuum, New York.

Jones, D., April 16, 2011. The free will delusion. New Science 210 (2808), 32–35.

Joyce, R., 2013. Ethics after Darwin. In: Ruse, M. (Ed.), The Cambridge Encyclopedia of Darwin and Evolutionary Thought. Cambridge University Press, Cambridge UK, pp. 461–467.

Kasturi, J.A., Viswanath, S., Kiulawan, A., Narine, R., 2014. A progressive Hindu approach to god. Tikkun 29 (3) (Summer) 36–37 and 67–68.

Lyotard, J., 1992. In: Pefanis, J., Thomas, M. (Eds.), The Postmodern Explained. University of Minnesota Press, Minneapolis.

Metzinger, T., 2009. The Ego Tunnel: The Science of the Mind and the Myth of the Self. Basic Books, New York.

Monod, J., 1972. Chance and Necessity. In: Wainhouse, A. (Ed.). Collins, London.

Mühling, M., 2014. Resonances: Neurobiology, Evolution and Theology. Vandenhoeck & Ruprecht, Göttingen.

Nagel, T., 2012. Mind and Cosmos: Why the Materialist Neo-darwinian Conception of Nature Is Almost Certainly Wrong. Oxford University, Oxford UK.

Peters, T., 2003. Science, Theology, and Ethics. Ashgate, Aldershot UK.

Rahner, K., 1988. Natural science and reasonable faith. In: Theological Investigation, vol. 21, pp. 16–55. New York: Crossroad, 1961–1988; XXI.

Rose, S., 2005. The 21st Century Brain. Jonathan Cape, London.

Roy, R., December 2005. Scientism and technology as religions. Zygon 40 (4), 835–844.

Ruse, M., 2013. Introduction. In: Ruse, M. (Ed.), The Cambridge Encyclopedia of Darwin and Evolutionary Thought. Cambridge University Press, Cambridge UK, pp. 1–31.

Tye, M. Qualia. In: Zalta, E.N. (Ed.), 2013. The Stanford Encyclopedia of Philosophy (Fall 2013). http://plato.stanford.edu/archives/fall2013/entries/qualia/.

Voegelin, E., 1956–1987. Order and History. 5 Volumes. Louisiana State University Press, Baton Rouge LA.

Whitehead, A.N., 1925/1953. Science and the Modern World. Cambridge University Press, Cambridge UK.

Wilson, E.O., 1975. Sociobiology: The New Synthesis. Harvard University Press, Cambridge MA.

Wilson, E.O., 2012. The Social Conquest of Earth. W.W. Norton, New York.

Chapter 42

Evolution and the Future of Medicine

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INTRODUCTION

There have been three major upheavals in the history of Western medicine. Each has changed how medical professionals treat patients, and how patients regard healthfulness. Is another change coming? We think there is. We believe that a fourth reformation of the practice of medicine is imminent, that it will be based on evolutionary genomics, and that it will happen before the end of the 21st century. This reformation is not just historically likely, but also desirable and necessary for the continued improvement of patient outcomes. With it will also arrive the possibility of reducing the aggregate costs of the practice of medicine.

We can't understand the significance of where medicine is headed without the context of past upheavals in the foundations of medicine, so we will begin by briefly offering our views on the overall arc of Western medicine to this point in time. Although the roots go back further to Egypt and Babylon, auspicious advances in medical understanding occurred during the classical Greek and Roman periods. An acknowledged early founder of the scientific method as well as anatomy and physiology, Herophilus of Chalcedon (335−280 BCE) did the first-known human anatomical dissections and with his student Erasistratus (304−ca.250 BCE) established the connection between mental functions and the brain; mapped sensory and motor neurons; studied metabolism; and gave names to many of the bones and muscles (Russo, 2004; see Nutton, 2013). In the autumn of Hellenistic science and of the Roman Empire, Galen of Pergamon (129−ca.217 CE) discovered the physiological functions of many of the organ systems, such as the renal system and the connection between speech and the brain (Siegel, 1968, 1970; 1973). Much of this knowledge was lost after the fall of the Roman Empire in the 5th century CE and through the medieval period, and recovery was slow and halting through the Renaissance (Russo, 2004). Only with the 16th century did major forward progress begin again.

The first of the three major historical reformations of Western medicine occurred 1500−1850. Around the time of the Reformation in Latin Christendom, when European surgeons, physicians, and naturalists were no longer constrained by medieval religious rules prohibiting dissection, they began to accumulate anatomical and crude physiological knowledge. Western medical scientists could at last learn by observation rather than by conjecture and extrapolation. Pulmonary respiration was described by Protestant dissident scholar and physician Miguel Servetus (unpublished, ca.1542), and later published within *Christianismi Restitutio* (1553). Soon afterward, he was burned at the stake near Calvinist Geneva after fleeing from both Protestant and Catholic authorities. Only three copies of the book escaped destruction (Hillar and Claire, 2002).

Later physicians and biologists still met with controversy, but most were not literally burned at the stake. William Harvey (1578−1657) was not the first in his field, but his dissections and descriptions of cardiovascular circulation in *De Motu Cordis* (1628) were the most detailed and definitive of his formative era. On the basis of such crude but essential physiological discoveries, Western medicine resumed progress. By the 19th century, physicians were able to use their new information and skills to save lives in at least some circumstances, if only by such elementary means as the use of efficient tourniquets to prevent bleeding out.

The second reformation of medicine is more famous. In the late 19th century, medical microbiology provided the intellectual framework and conceptual insights required to mitigate the spread of contagious disease. Early in the 19th century, the notion still lingered on that epidemic diseases such as bubonic plague, cholera, and malaria (literally, "sick air") were caused by miasma of the air, or by polluting fumes from filth and putrid decaying matter (Last, 2007; Karlen, 1995; Kokayeff, 2013). There had been

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00042-9

earlier hints that this might not be the case: in 1546, Girolamo Fracastoro proposed that seed-like disease contagions could be spread among people. In 1676, Anton van Leeuwenhoek empirically observed microorganisms through the microscope (Egerton, 2006), and earlier, in 1665, Robert Hooke had microscopically observed mold fruiting bodies (Gest, 2005). It is possible that a Jesuit priest, Athanasius Kirchner, was the first to see microorganisms, decades before the publication of Robert Hooke's *Micrographica* (Wainwright, 2003).

By 1700, physician Nicolas Landry had proposed that microscopic "worms" caused diseases such as smallpox (Crookshank, 1888). Botanist Richard Bradley, in 1720, suggested that microscopic "poisonous insects" caused plague and "all pestilential distempers" (Santer, 2009). By the late 19th century, botanist Ferdinand Cohn had classified bacteria by shape (Drews, 1999), and scientists of the day had a starting point for discussing their characteristics and role in the transmission of diseases.

Intellectual progress with the problem of contagious disease accelerated during the 19th century. The first to empirically link disease causally to a microorganism was Agostino Bassi, who showed in experiments from 1808 to 1813 that a "vegetable parasite" caused silkworms to contract the disease muscardine (Barbo, 1836), now understood to be fungal. Bassi went on to propose that many diseases of plants, animals, and humans are the result of infectious microscopic organisms. In 1847, the obstetric physician Ignaz Semmelweis linked the high puerperal fever infection rates in pregnant women to "cadaverous particles" (cited in István, 1983) on the unwashed hands of medical doctors returning from autopsies, in strong contrast with the much lower rates associated with those cared for by midwives (Hanninen et al., 1983). Dr. John Snow (1855) proposed that cholera was caused by drinking a contagion found in water. In 1854, Filippo Pacini discovered the microorganism responsible for cholera, *Vibrio cholera*, which was later rediscovered by Robert Koch (Howard-Jones, 1984; Bentivoglio and Pacini, 1995).

Starting in the 1850s, Pasteur experimentally established that microbial fermentation and growth in nutrient media do not result from spontaneous generation; he studied the etiology of puerperal fever; he discovered that microorganisms were responsible for spoilage in various types of drinks; and he introduced his namesake heat treatment, pasteurization, as a preventive measure (Pasteur, 1880; Ullmann, 2007). He linked two silkworm parasitic diseases, *pébrine* and *flacherie,* to egg-infecting parasites (Ullmann, 2007), and, building on others' work, Pasteur helped develop rabies and anthrax vaccines. Other notable advances of this era have also stood the test of time: German physician and microbialist Robert Koch linked microbial pathogens with specific diseases, and helped develop criteria, called Koch's Postulates or Koch-Henle Postulates, that have been adapted and remain informative in the study and treatment of infectious bacteriological disease (Brock, 1999). This microbial revolution in the understanding and treatment of infectious disease allowed physicians to save millions of lives during the 20th century.

The third reformation of medicine has chiefly taken place since 1950. The development of molecular biology has recast cell physiology within a molecular framework, eliminating many of the pre-1950 ideas about the foundations of chronic disease. In particular, the molecular genetic foundations of the "errors of metabolism" identified by Archibold Garrod in his 1923 book *Inborn Errors of Metabolism* have been discovered. The specific DNA sequence changes, as well as the downstream metabolic deficiencies, of numerous genetic diseases have been well characterized and can now be precisely diagnosed using molecular genetic assays. For example, cystic fibrosis is now known to be a result of disabling mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene (Rommens et al., 1989; Gadsby et al., 2006). This gene encodes a transmembrane ion transporter protein that, when so mutated, misfolds so as to interrupt many epithelial secretionary processes, with debilitating and life-threatening congestive results (Riordan et al., 1989; Childers et al., 2007). The cause of Huntington's Disease has been shown to be an excess of repeats of a glutamine-encoding cytosine-adenine-guanine codon near the 5′ end of the *huntingtin* (*HD* or *HTT*) gene (Huntington's Disease Collaborative Research Group, 1993; Choi et al., 2014; Harjes and Wanker, 2003; Goehler et al., 2004). We have made significant headway in characterizing other genetic diseases as well. The very rare Hutchinson−Gilford progeria syndrome (HGPS) mimics accelerated aging and causes early death, often by coronary arterial disease or stroke (McClintock et al., 2007). About 90% of progeria cases have a synonymous *G608G* (GGC > GGT) mutation in exon 11 of the lamin A/C (*LMNA*) gene, which activates a splice donor site, leading to the production of the pathological protein progerin (McClintock et al., 2007).

Characterizing diseases such as Huntington's and progeria at the molecular level is an important step toward treating and even preventing them. There have been cases in which uncovering the underlying biochemistry and molecular biology of particular genetic diseases has led directly to effective treatment. One example is the treatment of phenylketonuria by modifying diet to reduce phenylalanine exposure, notably after neonatal biochemical diagnosis.

This brief overview of prior landmark episodes in medical history shows significant reformation during distinctive episodes of scientific discovery and practical advocacy. It is far from the case that medicine has placidly progressed from its foundations in the classical era of Hippocrates.

We are not novel in proposing the need for a fourth reformation of medicine, one focusing on incorporating findings and directives from evolutionary biology. To give one such previous proposal, the idea of incorporating evolutionary biology in medicine was put forward with particular prominence, force, and eloquence by Nesse and Williams in their 1994 book, *Why We Get Sick: The New Science of Darwinian Medicine*. Our thoughts have developed in the light cast by that work.

Here we provide, first, a general discussion of the idea of evolutionary medicine; second, a discussion of the relevance of evolutionary genomic research to biomedical research and medical practice; third, an introduction to the relevance of "Hamiltonian" research to the prevention and treatment of chronic diseases of aging; and fourth, thoughts on the possibilities of using evolutionary genomic strategies for the development of pharmaceuticals.

THE IDEA OF EVOLUTIONARY MEDICINE

The basic idea of incorporating findings from evolutionary biology in medicine seems, at first, eminently reasonable. After all, the ecology and evolutionary genetics of a pathogen will often be key to the effective treatment of its infections in humans, as discussed in other chapters. Similarly, investigating the population genetics underlying the transmission and frequency of genetic diseases is a longstanding part of medical genetics. However, it is when we turn to chronic noninfectious diseases that now affect the majority of adults that things become trickier.

A Two Cultures Problem

There is a major problem inhibiting the introduction of evolutionary biology into the practice of medicine. Evolutionary biology is the most general, and the most theoretical, of all fields of life science. It focuses on large swaths of time, difficult mathematical theories, and now genome-wide patterns of genetic polymorphism. Among all academic fields within the life sciences, evolutionary biology is most comparable to physics in its aspirations toward strong inference tests of powerful yet general mathematical theories. In terms of Ernest Rutherford's aphorism that "all science is either physics or stamp-collecting," modern-day evolutionary biology falls on the physics side of that divide.

Medicine falls on the other side of the divide. The practice of medicine revolves around the correct inference of particular details of pathophysiology, singular diseases or syndromes, and specific infectious pathogens, together with the most effective choices of medication or procedure for treatment. Where evolutionary biology takes on the whole diversity of life, the concrete and narrowly focused subject of medicine is humans, their disorders, and their pathogens. This creates a "two cultures" problem, in which the fundamental approach and breadth of one field could not be more different from those of the other field. How can we construct a functional bridge across which the intellectual scope and powerful concepts of evolutionary biology can be transported into the realm of medicine?

Two Strategies for Bridging Biological Cultures

The idea of evolutionary medicine is hardly a secret, and there are symposia where evolutionary biologists and biomedical academics propose new therapeutic approaches to specific pathogens and chronic disorders based on relatively narrow hypotheses derived from evolutionary research or speculations (Stearns and Koella, 2007). However, many of these attempts to bridge the evolutionary and medical cultures are in effect Darwinian supplementation, rather than fundamental reform, of medical research and practice. Although the reductionist theorists of modern medicine may disparage such efforts, practicing physicians who have experienced the limitations and failures of reductionist dogmas firsthand may be more open-minded.

Applying Darwinian evolution to medicine is still a tenuous and not yet systemic endeavor, although the potential for success is increasing as awareness of the benefits of cross-cultural scientific collaboration increases. Interest in finding ways to apply evolution to medicine has been around since the late 19th century (Zampieri, 2009), and there is a growing effort toward systematically reorganizing medicine in an evolutionary framework (Shanks and Pyles, 2007; Román-Franco, 2009).

One area in which there has been some useful integration of evolutionary biology into medicine has been in the study of adaptive immunity. Immunologist Niels Jerne (1955) proposed that there are a large variety of globulin antibody molecules continuously synthesized, some fraction of which possess chemical affinity toward any antigen entering the blood or lymph. Physician David Talmage (1957) further argued that successful antibody–antigen conjugates formed on the surface of specific cells producing the antibody caused the proliferation of such cells. Building on Jerne and Talmage, Macfarlane Burnet (1959) developed the "clonal selection" theory of how "antigentic determinants" trigger antibody-producing cell proliferation, including long-term immunological memory, through differential affinities to the antigen in question. This hypothesis also began to crack the door toward understanding autoimmune disease.

Today, in the age of genomics, we are beginning to recognize what was far beyond the imagination of Jerne, Talmage, Burnet, and other early students of adaptive immunity: Darwinian evolution has had a direct hand in immune adaptation. For instance, we now see that the great

diversity of antibody production in the lymphocytic V(J)D system is tied to recombination-activating genes (*RAG1* and *RAG2*), the first of which is homologous to a recombinase found in transposons (Kapitonov and Jurka, 2005), genomic hitchhikers from evolutionarily ancient infections. Phylogenomic analysis is now probing the evolutionary histories of the genes that encode the antigen presentation and processing system (Forni et al., 2014). Further advances of evolutionary theory in immunology with direct medical applications are likely to follow in unforeseen ways.

We certainly do not wish to impede even piecemeal accretions of evolutionary research within a medical context, but there is an alternative to incremental and haphazard progress. Thinking about the three major reformations of medical practice during the past 500 years, we note that they hinged on eliminating well-established but materially erroneous dogmas. For example, Pasteur and his followers fought avidly against the inclination of most physicians of the day to ignore the importance of microbial contamination. That is to say, intellectual revolutions in biology were eventually followed by substantive revolutions in medical education and practice, despite the characteristic resistance the medical establishment has shown toward such innovation and extirpation. Here we propose that a fourth large-scale reformation of medicine should follow from the introduction of evolutionary thinking into medical education and practice.

AN EVOLUTIONARY PERSPECTIVE ON GENOMIC MEDICINE

The Failed Promise of Reductionist Genomics

When James Watson and others were avidly selling the idea of the Human Genome Project to their skeptical colleagues and to Congress, they broadly suggested that learning the genomic master programs of life, particularly that of the human species, would make understanding and treating disease vastly easier. In effect, they promised, once we know the entirety of the DNA sequence of the human genome, reading off the key sites controlling medical disorders will become straightforward, with powerful new treatments to follow shortly thereafter.

Nothing like that has happened. Straightforward solutions to medical problems did not come from the first two human genomes fully sequenced in 2003. Nor have they since come from the thousands of human genomes analyzed in Genome-Wide Association Studies (GWAS) of chronic diseases. It has all turned out to be much more difficult than Watson and the other molecular biologists anticipated, with much more causal complexity and subtlety. While the sequencing of thousands or indeed hundreds of thousands of human genomes will add enormously to our understanding of human evolution, medical diagnosis and practice have not been obviously illuminated by this avalanche of detailed information about the human genome. The advent of genome-wide sequencing and analysis has been arguably the most radical transformation of the empirical foundations of biology in its entire history, but the immediate medical revolution that was so confidently prophesied has not materialized.

An Evolutionary Alternative to Reductionist Genomics

Evolutionary geneticists are now in the business of parsing the complexity of genomes with respect to both (1) the evolution of such genomes and (2) how genomes produce phenotypes. We already know that there is a vast amount of genetic polymorphism in the genomes of humans and other outbred animals, such as natural populations of the fruit fly *Drosophila melanogaster*. GWAS are beginning to show that a stunningly large amount of human genetic polymorphism is functionally significant (eg, Welcome Trust Case Control Consortium, 2007; the ENCODE project). Unfortunately, the analysis of standing genetic variation using genome-wide technologies has proven much less penetrating than was hoped (Rose et al., 2011; Burke et al., 2014). It has not revealed the master controls that underlie either organismal function or medical pathology, except in cases involving the mutations underlying certain severe genetic diseases such as Huntington's Disease, progeria, and cystic fibrosis.

Evolutionary biologists also perform GWAS analyses and add to it experimental evolution to amplify genetic differentiation. Experimental evolutionary genomics has proven an exceptionally useful tool for parsing the genomic foundations of both function and dysfunction in model species, from *Escherichia coli* to *Drosophila melanogaster*. This approach is illustrated well by a study of the genomic foundations of adaptation to elevated temperature in *E. coli.,* in which Tenaillon et al. (2012) propagated more than 100 replicate populations of *E. coli* for 2000 generations at high temperatures. Then they sequenced one genome from each of these replicate populations at the end of selection. All replicate populations achieved high levels of adaptation to high temperature conditions, but the pattern of gene sequence evolution was much more complex. In total, 1331 DNA sequence changes were found across the ensemble of populations, with more than 600 different sites undergoing evolutionary change identified. While adaptation to high temperatures repeatedly employed common pathways, the genetic details of what just 2000 bacterial generations had accomplished were far more

complex than expected in conventional scenarios for the genetic foundations of adaptation in bacteria. Bacterial genomes are orders of magnitude simpler than those of multicellular animals like humans. The complexity of the genomics of bacterial adaptation to elevated temperature sets a minimum level for what we can expect for the genomics of human function and disorders.

The combination of experimental evolutionary genomics with phylogenetic tools allows evolutionary geneticists to parse the human genome. Many of the genomic sites with functionally important genetic variation for experimental evolution in animals like *Drosophila* are embedded in sequences that have close homologues in human populations. This lets us combine experimental evolutionary genomics in model animal species with information about the human genome in order to approach human medical problems with far greater scientific penetration than ever before. In effect, experimental evolution can serve as a key to unlock the functional mysteries of model animal species genomes and then, of most medical interest, the genomes of patients. At present, the use of this strategy is just getting started. Highly provisional results linking *Drosophila* experimental evolutionary genomic findings to human GWAS have been sketched out in the context of the chronic diseases of aging (Rose et al., 2010).

A HAMILTONIAN APPROACH TO THE CHRONIC DISEASES OF AGING

Aging: A Reductionist Failure

In no area has the inadequacy of reductionist biomedical research been more obvious than in the study of aging. Although it has proven possible for molecular geneticists to construct mutant yeast and nematodes with greatly extended longevities, these organisms characteristically have reduced reproduction, mobility, competitive ability, and/or cognition (Van Voorhies et al., 2006; Bansal et al., 2015). In effect, lifespan is increased, but what we will call *healthspan* is diminished. This singular defect of this large-effect mutation strategy dissuades most, though not all, gerontologists from recommending comparable molecular interventions for chronic human disorders.

The Evolutionary Solution to the Scientific Problem of Aging

Building on the verbal sketches of R. A. Fisher, P. B. Medawar, and G. C. Williams, in 1966 W. D. Hamilton formulated the beginnings of a mathematical theory for the evolution of aging based on declining forces of natural selection with adult age. From 1970 to 1980, Brian Charlesworth developed this body of theory to a satisfactory level (eg, Charlesworth, 1980), making the mathematical theory for the explanation of aging among the strongest examples of biological theory in general. There have been many elaborations of this core theory, particularly with respect to the evolution of very late life history (eg, Mueller et al., 2011), but the core mathematical theory developed by Hamilton and Charlesworth is still central to most theoretical analyses of aging within evolutionary biology.

The Hamiltonian theory of aging has been the chief foundation of evolutionary research on aging, or senescence, since about 1980. Experimental work has clearly corroborated the Hamiltonian explanation for aging, not least by the simplicity of producing animals with longer healthspans by manipulating Hamilton's forces of natural selection, by shifting reproductive windows in evolving populations (Rose, 1991; Rose et al., 2004). As a body of research in evolutionary biology, Hamiltonian studies of aging provide one of the more important and likely candidates for insertion into the corpus of medical research and practice.

Applying Hamiltonian Research to Human Chronic Disease

Age-related diseases such as cardiovascular disease and type 2 diabetes are proliferating globally. For this reason, the strategy of applying the well-founded discoveries of evolutionary research on aging seems not merely reasonable but imperative. However, such application quickly runs into problems arising from the ad hoc or supplementary invocation of evolution in discussions of health and disease.

Loren Cordain and others (O'Keefe and Cordain, 2004; Jönsson et al., 2009; Lindeberg, 2010; De Vany and Taleb, 2011) have invoked evolutionary thinking in their claims that adopting a hunter-gatherer diet will alleviate chronic disorders, and there have been medical case histories seemingly supporting these claims. Indeed, medical anthropologists have shown repeatedly that individuals with hunter-gatherer ancestry might alleviate their chronic midlife medical disorders by switching back to their ancestral diets (for example, Lindeberg, 2010). However, evolutionary experiments using model organisms such as *D. melanogaster* have shown extensive adaptation to novel diets within a small number of generations (Matos et al., 1999; Simões et al., 2008). Research with urea supplementation in *Drosophila* provides a clear example of adaptation to noxious novel foods proceeding quickly. Borash et al. (2000) studied the developmental viability of *D. melanogaster* populations selected for urea tolerance. When reared as larvae on urea-supplemented media, females and males from the urea-selected populations developed much more successfully.

This seemingly implies that human populations that have long practiced agriculture should be well adapted to the agricultural diet and lifestyle, as Zuk (2013) has proposed. She contends that human populations that have practiced agriculture for 200–400 generations have had sufficient evolutionary time to adapt to an agricultural diet. Zuk draws particular attention to the evidence for adaptation to milk consumption among European adults, such as the continued activity of the lactase enzyme at later ages in European populations.

If human populations that have long practiced agriculture are well adapted to the agricultural diet and lifestyle, as Zuk argues, how is it that adopting a hunter-gatherer diet alleviates chronic disorders, as clinical studies have shown (Lindeberg, 2010)? Hamiltonian evolutionary theory can resolve this apparent contradiction. Strong forces of natural selection at early ages have provided young humans with long agricultural ancestry reasonable health under agricultural conditions. Nonetheless, the decline of Hamilton's forces at later ages can lead to a mismatch with the agricultural diet at later ages.

To illustrate this principle in a simple example: approximately 10,000 years ago, a child introduced to wheat, rice, or corn would not likely have had the metabolic equipment necessary to process and utilize these agricultural foods. As a result, that child would have been more likely to become malnourished and more likely to succumb to infection than a child who did happen to have the metabolic enzymes to thrive on this novel diet. The healthy and strong child would have been more likely to live on to reproduce and pass on the genes for these metabolic enzymes, allowing direct descendants to not only tolerate this diet, but to thrive at early ages, and even into young adulthood. This effect would have become stronger over subsequent generations with progressively greater dependence on agricultural foods, and more and more individuals would have been able to tolerate and thrive on an agricultural diet during childhood and early adulthood.

The process of selection that sieves out those alleles that prevent us from thriving on agricultural foods becomes weaker as we get older, and then grinds to a halt after the average age at which populations stop reproducing. In much the same way that many individuals lose their tolerance to lactose at later ages of life, many begin to lose their tolerance to agricultural foods in and around their 30s or 40s. Thus, a more complete evolutionary analysis suggests that patients with chronic aging-related diseases such as arthritis, diabetes, hypertension, and hypercholesterolemia, should adopt a more Paleolithic diet and lifestyle specifically at later ages, even if they have a long agricultural ancestry (Mueller et al., 2011, Chapter 11). In addition to these disorders, perhaps even insomnia and depression might be addressed by a change to an ancestral diet.

STRATEGIES FOR PHARMACEUTICAL DEVELOPMENT

The Impasse Facing Reductionist Pharmaceutical Research and Development for Chronic Disorders

Genomic analysis of functional characters, from height in humans (eg, Yang et al., 2010) to developmental speed in fruit flies (Burke et al., 2010), has revealed the functional involvement of many genomic sites, from hundreds to thousands. Given the number of sites involved and the rarity of major effect loci identified in these studies, it is likely that most chronic diseases are affected by genetic variation of small effect at many genomic loci.

The traditional reductionist pharmaceutical research and development (R&D) strategy focuses on a small number of pathways for disease etiology; often, on just one pathway. Type 1 diabetes, as an exemplar, is a disorder involving complete, or almost complete, failure of insulin production. The intravenous supply of insulin is the medical intervention of choice, in order to approximate functional regulation of serum glucose. A single protein biosynthetic failure is countered by providing that protein. In this case, there is a single defective pathway that is treated by the provision of a single substance. But of all the cases of chronic diabetes, type 1 diabetes affects just a small minority of patients, from as much as 6 per 10,000 in European children to about one-hundredth that rate among children in India (Gale, 2012), although failures of diagnosis may contribute to this disparity.

By contrast, according to the World Health Organization, "347 million people worldwide have diabetes, 90% of whom have type 2 diabetes" (World Health Organization, 2014). Type 2 diabetes is a disorder characterized by insensitivity to insulin. That is, insulin is produced but does not effectively regulate serum glucose levels. The resulting chronic elevation of serum glucose levels in turn leads to progressive damage to multiple tissues. From a Hamiltonian perspective, type 2 diabetes is a chronic disorder among adults that is strongly affected by lifestyle factors, improving in incidence or progression with higher activity levels, lower body weight, and/or a diet low in carbohydrates. That is, modification of the 20th century sedentary lifestyle reliant on processed foods reduces the likelihood of type 2 diabetes, even among those diagnosed with prediabetic elevation of serum glucose levels. In contrast to the effectiveness of lifestyle changes, the pharmaceutical treatment of type 2 diabetes is only moderately successful. Medications such as metformin (Glumetza, Fortamet,

Riomet, Glucophage) slow its progression, but do not entirely eliminate the pathophysiology of the disorder. Characteristically, such medications lose effectiveness over time. In conventional medical thought, medications prescribed for a specific ailment are simple solutions to a singular disorder. Any other effects are considered "side effects," and are of a lesser and secondary impact on nonessential systems. But in practice, that is not always the case; for example, antipsychotics used extensively to treat schizophrenia, various affect disorders, anxiety, and insomnia can accelerate the progression of type 2 diabetes. This occurs as a result of metabolic syndrome, a known effect of some antipsychotics, which consists of obesity, high cholesterol, and diabetes. In particular, antipsychotics such as olanzapine, quetiapine, and clozapine, can lead to the development of type 2 diabetes.

A number of biochemical pathways are known to affect type 2 diabetes, such as PPAR-ɣ, which serve as targets for the development of medication (Bermúdez et al., 2010). But the genomic analysis of type 2 diabetes suggests that there are many genomic sites that affect its incidence (eg, Huang et al., 2014; Kong et al., 2014; Padmalayam, 2014; Grover et al., 2014). A problem facing the treatment of type 2 diabetes is that the disorder involves numerous biochemical mechanisms, each of which is likely to have only a small effect on the incidence and progression of the disorder. How can pharmaceuticals be developed that can simultaneously target the many components of the complex underlying machinery of this, or other similarly complex, disorder? There is no certainty that a candidate medication that targets just one of these pathways can be effectively combined with medications that target other pathways that underlie type 2 diabetes. The complexity of the drug trials that would be required to best calibrate this polypharmacy is daunting.

The Impasse Facing Evolutionary-Genomic Pharmaceutical Research and Development for Aging

An emerging cliché of health advocacy is the idea of "treating aging," as chronic disorders such as type 2 diabetes, hypertension, high cholesterol, and chronic back and joint pain all show a striking pattern of age association. That is, numerous chronic disorders have incidence patterns that correlate with biological age, particularly after age 30. Cardiovascular diseases such as atherosclerosis, which is not due to mechanical trauma, and cancers other than those such as retinoblastoma, which is due to a rare genotype, have patterns of incidence that increase exponentially with adult age. Thus, it is now commonly argued by gerontologists that these aging-associated diseases are caused by a common underlying physiological progression that defines aging itself.

In contrast to the conclusions of present-day gerontologists, evolutionary biologists argue that aging is not a physiological process any more than adaptation itself is (eg, Mueller et al., 2011; Rose et al., 2012). Rather, evolutionary biologists consider aging to be a pattern of age-dependent detuning of adaption. In this view, there is no underlying physiological process of aging whatsoever, turning the notion of "treating aging" on its ear, and making the proposal to treat that conjectural process, rather than the secondary chronic disorders that it engenders, impracticable.

This does not mean that evolutionary biologists have less interest in mitigating the effects of aging; rather, we have very different strategies for retuning age-dependent adaptation so as to postpone if not effectively eliminate aging and its attendant chronic disorders (eg, Rose et al., 2014). After all, evolutionists have been deliberately postponing and slowing aging using experimental evolution for decades (eg, Rose et al., 2004). Rose et al. (2010) presented, in reasonable detail, one such strategy for mitigating human aging, using genetic homologies between the experimental evolutionary genomics of aging in fruit flies and the genomics of human chronic age-associated diseases such as type 2 diabetes.

Problems with evolutionary genomic proposals should be noted carefully. First, such proposals face the problem of trying out many combinations of multiple candidate substances that might affect underlying pathways identified by genomic analysis, just like reductionist pharmaceutical R&D strategies. Second, in the absence of a comprehensive and detailed understanding of the physiological genomics that underlie the tuning of human age-dependent adaptation, it would be very difficult to choose candidate substances to test in any such massive drug trials. This suggests that there are decades of additional research ahead before the advent of the systems biology models of human age-dependent adaptation required to refashion human aging (Rose et al., 2014). The direct approach to the study of human aging that evolutionary research on aging suggests is possible might not be a practicable strategy for some time to come. Eventually it should yield to the advancing tools of network analysis of big data, but that is not an immediate prospect.

A Promising Middle Way?

A less-noticed feature of research using experimental evolution is that it can be somewhat narrowly focused. The classic studies on the evolution of age-dependent or environment-dependent adaptation focused on fitness itself (eg, Lenski et al., 1991) or its life-historical components (eg, Rose, 1984). But experimental evolution can be applied to any characteristic that can be used as a focus of selection, from resistance to acute lethal stressors

(eg, Rose et al., 1992) to running behavior (eg, Swallow et al., 2009).

The physiological mechanics of slowed aging in fruit flies have been studied using selection experiments focused on bits of that physiological machinery separately (Rose et al., 2004). For example, a characteristic feature of slowed aging in experimentally evolved fruit flies is increased desiccation resistance (Service et al., 1985). Selecting for increased desiccation resistance in turn increases lifespan (Rose et al., 1992). The physiological characteristics that underpin increased desiccation resistance are increased water content and reduced rates of water loss (Chippindale et al., 1998). These two characteristics in turn evolve independently from each other (Archer et al., 2007). Therefore, if we were interested in pharmaceutically increasing desiccation resistance in fruit flies, we could focus on increasing their water content and reducing their rate of water loss. This is a more tractable problem than finding medications that affect the fly aging pattern as a whole (Matsagas et al., 2009; Rose et al., 2010). The choice of such pharmaceutical candidates could in turn be guided by genomic analysis of fruit fly populations that have evolved high levels of desiccation resistance.

We are not particularly interested in augmenting desiccation resistance in fruit flies as an end point. However, fruit flies also show progressive heart disease as a function of age (Nishimura et al., 2011; Ocorr et al., 2007a,b), and fruit flies that have evolved greater lifespans have more robust hearts (Shahrestani et al., in preparation). Furthermore, conventional genetic analysis of loci like *opa1* has already revealed similarities between the genetic foundations of heart disease in humans and in fruit flies (eg, Shahrestani et al., 2009). This suggests that we could use a more focal evolutionary genomic strategy to develop medications for specific chronic disorders such as heart disease, taking advantage of genetic similarities between fruit flies and humans whenever they are found. Such a strategy could proceed by selecting for enhancements of characteristics such as heart robustness in *Drosophila.* These fruit flies could then be genomically analyzed using sequencing of DNA or analyses of gene expression. As proposed by Rose et al. (2010), the loci identified by experimental evolution could then be tested for both genetic and functional parallels in patient populations, as is now done for candidate loci of major effect in studies of mutant model organisms. The loci identified using experimental evolutionary genomics could then be used as sources of information for choosing candidate pharmaceuticals. Initial rounds of testing could proceed in the model organism, rather than on patient populations, reducing expense and accelerating the R&D process.

Medications developed using this strategy are unlikely to provide the complete and general cessation of aging sought by some advocates of radical life extension (eg, de Grey and Rae, 2007). As has previously been argued (eg, Rose et al., 2014), the elimination of aging is probably decades away. But focal medications for chronic disorders could substantially extend survival and function, and in turn quality of life, beyond the benefits achievable using Hamiltonian lifestyle and diet modification.

CONCLUSION: A FOURTH RE-VISIONING OF MEDICINE

The piecemeal insertion of ideas from evolutionary biology into medicine will continue. These ideas are in vogue and provide decent sound bites, so they are able to garner public attention regardless of their legitimacy. However, merely transferring sporadic insights from evolutionary biology to medicine, while intermittently useful, can also generate confusion among both physicians and patients. We propose that a more useful strategy would be the wholesale re-visioning of medicine within an evolutionary context. Reductionist assumptions underlying medical practice and pharmaceutical development will continue to be challenged by the complexity of the genomics of human pathophysiology. These challenges will be increased by the fact that medical research into aging has made some fundamental errors in characterizing its actual causes and nature. To achieve the best patient outcomes, the evolutionary reformulation of the foundations of medicine should be thoroughgoing, careful, and systematic. We do not claim to have achieved anything like that here. But we hope that we have identified the need for such reformation, as well as some of its promise.

REFERENCES

Archer, M.A., Bradley, T.J., Mueller, L.D., Rose, M.R., 2007. Using experimental evolution to study the physiological mechanisms of desiccation resistance in *Drosophila melanogaster*. Physiological and Biochemical Zoology 80 (4), 386−398. http://dx.doi.org/10.1086/518354.

Bansal, A., Zhu, L.J., Yen, K., Tissenbaum, H.A., 2015. Uncoupling lifespan and healthspan in *Caenorhabditis elegans* longevity mutants. Proceedings of the National Academy of Sciences of the United States of America 112 (3), E277−E286.

Barbo, J., 1836. De la muscardine (maladie des vers à soie). Bonbée, Paris, France.

Bentivoglio, M., Pacini, P., 1995. Filippo Pacini: a determined observer. Brain Research Bulletin 38 (2), 161−165. http://dx.doi.org/10.1016/0361-9230(95)00083-Q.

Bermúdez, V., Finol, F., Parra, N., Parra, M., Pérez, A., Peñaranda, L., Vílchez, D., Rojas, J., Arráiz, N., Velasco, M., 2010. PPAR-gamma agonists and their role in type 2 diabetes mellitus management.

American Journal of Therapeutics 17 (3), 274–283. http://dx.doi.org/10.1097/MJT.0b013e3181c08081.

Borash, D.J., Pierce, V.A., Gibbs, A.G., Mueller, L.D., 2000. Evolution of ammonia and urea tolerance in *Drosophila melanogaster*: resistance and cross-tolerance. Journal of Insect Physiology 46 (5), 763–769.

Brock, T.D., 1999. Robert Koch: A Life in Medicine and Bacteriology. American Society of Microbiology Press, Washington, DC.

Burke, M.K., Dunham, J.P., Shahrestani, P., Thornton, K.R., Rose, M.R., Long, A.D., 2010. Genome-wide analysis of a long-term evolution experiment with *Drosophila*. Nature 467 (7315), 587–590.

Burke, M.K., King, E.G., Shahrestani, P., Rose, M.R., Long, A.D., 2014. Genome-wide association study of extreme longevity in *Drosophila melanogaster*. GBE 6 (1), 1–11. http://dx.doi.org/10.1093/gbe/evt180.

Burnet, F.M., 1959. The Clonal Selection Theory of Acquired Immunity. Vanderbilt University Press, Nashville, TN.

Charlesworth, B., 1980. Evolution in Age-structured Populations. Cambridge University Press, Cambridge, UK.

Childers, M., Eckel, G., Himmel, A., Caldwell, J., 2007. A new model of cystic fibrosis pathology: lack of transport of glutathione and its thiocyanate conjugates. Medical Hypotheses 68 (1), 101–112.

Chippindale, A.K., Gibbs, A.G., Sheik, M., Yee, K.J., Djawdan, M., Bradley, T.J., Rose, M.R., 1998. Resource acquisition and the evolution of stress resistance in *Drosophila melanogaster*. Evolution 52 (5), 1342–1352. http://dx.doi.org/10.2307/2411304.

Choi, Y.B., Kadakkuzha, B.M., Liu, X.A., Akhmedov, K., Kandel, E.R., Puthanveettil, S.V., 2014. Huntingtin is critical both pre- and postsynaptically for long-term learning-related synaptic plasticity in *Aplysia*. PLoS One. http://dx.doi.org/10.1371/journal.pone.0103004.

Crookshank, E., 1888. The history of the germ theory. BMJ 1 (1415), 312.

de Grey, A., Rae, M., 2007. Ending Aging: The Rejuvenation Breakthroughs That Could Reverse Human Aging in Our Lifetime. St. Martin's Press, New York, NY.

De Vany, A., Taleb, N.N., 2011. The New Evolution Diet: What Our Paleolithic Ancestors Can Teach Us About Weight Loss, Fitness, and Aging. Rodale Press (incorporated).

Drews, G., 1999. Ferdinand Cohn, among the founders of microbiology. ASM News 65 (8), 547.

Egerton, F.N., 2006. A history of the ecological sciences, Part 19: Leeuwenhoek's microscopic natural history. Bulletin of the Ecological Society of America 87, 47. http://dx.doi.org/10.1890/0012-9623(2006)87[47:AHOTES]2.0.CO;2.

Forni, D., Cagliani, R., Tresoldi, C., Pozzoli, U., De Gioia, L., Filippi, G., Riva, S., Menozzi, G., Colleoni, M., Biasin, M., Lo Caputo, S., Mazzotta, F., Giacomo, P., Comi, G.P., Bresolin, N., Clerici, M., Sironi, M., 2014. An evolutionary analysis of antigen processing and presentation across different timescales reveals pervasive selection. PLoS Genetics 10 (3), e1004189. http://dx.doi.org/10.1371/journal.pgen.1004189.

Fracastoro, G., 1546. De contagione et contagiosis morbis (Wilmer Cave Wright (1930), Trans.). G. P. Putnam, New York, NY.

Gadsby, D.C., Vergani, P., Csanády, L., 2006. The ABC protein turned chloride channel whose failure causes cystic fibrosis. Nature 440 (7083), 477–483.

Gale, E.A.M., 2012. Epidemiology of Type 1 Diabetes. Diapedia, 2104085168 rev. no. 39: http://www.diapedia.org/type-1-diabetes-mellitus/epidemiology-of-type-1-diabetes (cited 09.08.14.).

Garrod, A.E., 1923. Inborn Errors of Metabolism. H. Frowde and Hodder & Stoughton, London, UK.

Gest, H., 2005. The remarkable vision of Robert Hooke (1635–1703): first observer of the microbial world. Perspectives in Biology and Medicine 48 (2), 266–272. http://dx.doi.org/10.1353/pbm.2005.0053.

Goehler, H., Lalowski, M., Stelzl, U., Waelter, S., Stroedicke, M., Worm, U., Droege, A., Lindenberg, K.S., Knoblich, M., Haenig, C., Herbst, M., Suopanki, J., Scherzinger, E., Abraham, C., Bauer, B., Hasenbank, R., Fritzsche, A., Ludewig, A.H., Büssow, K., Coleman, S.H., Gutekunst, C.A., Landwehrmeyer, B.G., Lehrach, H., Wanker, E.E., 2004. A protein interaction network links GIT1, an enhancer of huntingtin aggregation, to Huntington's disease. Molecular Cell 15 (6), 853–865.

Grover, M.P., Ballouz, S., Mohanasundaram, K.A., George, R.A.H., Sherman, C.D., Crowley, T.M., Wouters, M.A., 2014. Identification of novel therapeutics for complex diseases from genome-wide association data. BMC Medical Genomics 7 (Suppl. 1), S8. http://dx.doi.org/10.1186/1755-8794-7-S1-S8. Epub 2014 May 8.

Hamilton, W.D., 1966. The moulding of senescence by natural selection. Journal of Theoretical Biology 12 (1), 12–45. http://dx.doi.org/10.1016/0022-5193(66)90184-6.

Hanninen, O., Farago, M., Monos, E., 1983. Ignaz Philipp Semmelweis, the prophet of bacteriology. Infection Control 4 (5), 367–370.

Harjes, P., Wanker, E.E., 2003. The hunt for huntingtin function: interaction partners tell many different stories. TIBS 28 (8), 425–433.

Hillar, M.A., Claire, S., 2002. Michael Servetus: Intellectual Giant, Humanist, and Martyr. University Press of America, Lanham, MD, p. 95.

Howard-Jones, N., 1984. Robert Koch and the cholera *Vibrio*: a centenary. BMJ 288, 379–381.

Huang, T., Sun, J., Chen, Y., Xie, H., Xu, D., Li, D., 2014. Associations of common variants in methionine metabolism pathway genes with plasma homocysteine and the risk of type 2 diabetes in Han Chinese. Journal of Nutrigenetics and Nutrigenomics 7 (2), 63–74.

István, B., 1983. Ignaz Phillip Semmelweis 1818–1865. Druckerei Kner, Gyomaen drőd. Corvina Kiadó, Hungary.

Jerne, N.K., 1955. The natural-selection theory of antibody formation. Proceedings of the National Academy of Sciences of the United States of America 41 (11), 849–857.

Jönsson, T., Granfeldt, Y., Ahrén, B., Branell, U., Pålsson, G., Hansson, A., Söderström, M., Lindeberg, S., 2009. Beneficial effects of a Paleolithic diet on cardiovascular risk factors in type 2 diabetes: a randomized cross-over pilot study. CVD 8, 35.

Kapitonov, V.V., Jurka, J., 2005. RAG1 core and V(D)J recombination signal sequences were derived from Transib transposons. PLoS Biology 3 (6), e181. http://dx.doi.org/10.1371/journal.pbio.0030181.

Karlen, A., 1995. Man and Microbes: Disease and Plagues in History and Modern Times. Touchstone Book, Simon & Schuster, NewYork, NY.

Kokayeff, N., 2013. Dying to be discovered: miasma vs. germ theory. ESSAI 10. Article 24.

Kong, X., Zhang, X., Zhao, Q., He, J., Chen, L., Zhao, Z., Li, Q., Ge, J., Chen, G., Guo, X., Lu, J., Weng, J., Jia, W., Ji, L., Xiao, J., Shan, Z., Liu, J., Tian, H., Ji, Q., Zhu, D., Zhou, Z., Shan, G., Yang, W., 2014. Obesity-related genomic loci are associated with type 2 diabetes in a Han Chinese population. PLoS One 9 (8), e104486. http://dx.doi.org/10.1371/journal.pone.0104486.

Last, J.M. (Ed.), 2007. A Dictionary of Public Health. Oxford University Press. http://www.oxfordreference.com/view/10.1093/acref/9780195160901.001.0001/acref-9780195160901.

Lenski, R.E., Rose, M.R., Simpson, S.C., Tadler, S.C., 1991. Long-term experimental Evolution in *Escherichia coli*. I. Adaptation and divergence during 2,000 generations. American Naturalist 138 (6), 1315–1341. http://dx.doi.org/10.2307/2462549.

Lindeberg, S., 2010. Food and Western Disease. Health and Nutrition From an Evolutionary Perspective. Wiley-Blackwell.

Matos, M., Rose, M.R., Pité, M.T.R., Rego, C., Avelar, T., 1999. Adaptation to the laboratory environment in *Drosophila subobscura*. Journal of Evolutionary Biology 13 (1), 9–19. http://dx.doi.org/10.1046/j.1420-9101.2000.00116.x.

Matsagas, K., Lim, D.B., Horwitz, M., Rizza, C.L., Mueller, L.D., Villeponteau, B., Rose, M.R., 2009. Long-term functional side-effects of stimulants and sedatives in *Drosophila melanogaster*. PLoS One 4 (8), e6578. http://dx.doi.org/10.1371/journal.pone.0006578.

McClintock, D., Ratner, D., Lokuge, M., Owens, D.M., Gordon, L.B., Collins, F.S., Djabali, K., 2007. The mutant form of lamin A that causes Hutchinson-Gilford progeria is a biomarker of cellular aging in human skin. PLoS One 2 (12), e1269. http://dx.doi.org/10.1371/journal.pone.0001269.

Mueller, L.D., Rauser, C.L., Rose, M.R., 2011. Does Aging Stop? Oxford University Press, New York, NY.

Nesse, R.M., Williams, G.C., 1994. Why We Get Sick: The New Science of Darwinian Medicine. Times Books, a division of Random House, New York, NY.

Nishimura, M., Ocorr, K., Bodmer, R., Cartry, J., 2011. *Drosophila* as a model to study cardiac aging. Experimental Gerontology 46, 326–33010, 1016/j.exger.2010.11.035.

Nutton, V., 2013. Ancient Medicine (Sciences of Antiquity Series, second ed. Routledge, Taylor & Francis Group, London, UK.

O'Keefe, J.H., Cordain, L., 2004. Cardiovascular disease resulting from a diet and lifestyle at odds with our paleolithic genome: how to become a 21st-century hunter-gatherer. Mayo Clinic Proceedings 79, 101–108.

Ocorr, K., Akasaka, T., Bodmer, R., 2007a. Age-related cardiac disease model of *Drosophila*. Mechanisms of Ageing and Development 128, 112–116. http://dx.doi.org/10.1016/j.mad.2006.11.023.

Ocorr, K., Perrin, L., Lim, H.Y., Qian, L., Wu, X., Bodmer, R., 2007b. Genetic control of heart function and aging in *Drosophila*. Trends in Cardiovascular Medicine 17 (5), 177–182.

Padmalayam, I., 2014. The heat shock response: its role in pathogenesis of type 2 diabetes and its complications, and implications for therapeutic intervention. Discovery Medicine 18 (97), 29–39.

Pasteur, L., 1880. On the extension of the germ theory to the etiology of certain common diseases (trans.). In: Comptes Rendus, de l'Académie des Sciences, vol. xc. The University of Adelaide, pp. 103–144 (H.C. Ernst, M.D., Trans.). https://ebooks.adelaide.edu.au/p/pasteur/louis/exgerm/complete.html.

Riordan, J.R., Rommens, J.M., Kerem, B., Alon, N., Rozmahel, R., Grzelczak, Z., Zielenski, J., Lok, S., Plavsic, N., Chou, J.L., 1989. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. Science 245 (4922), 1066–1073.

Román-Franco, A.A., 2009. Medicine in the 21st century: towards a Darwinian medical epistemology. Puerto Rico Health Sciences Journal 28 (4), 345–351.

Rommens, J.M., Iannuzzi, M.C., Kerem, B., Drumm, M.L., Melmer, G., Dean, M., Rozmahel, R., Cole, J.L., Kennedy, D., Hidaka, N., 1989. Identification of the cystic fibrosis gene: chromosome walking and jumping. Science 245 (4922), 1059–1065.

Rose, M.R., Vu, L.N., Park, S.U., Graves Jr., J.L., 1992. Selection on stress resistance increases longevity in *Drosophila melanogaster*. Experimental Gerontology 27 (2), 241–250. http://dx.doi.org/10.1016/0531-5565(92)90048-5.

Rose, M.R., Passananti, H.B., Matos, M., 2004. Methuselah Flies: A Case Study in the Evolution of Aging. World Scientific Publishing, Singapore.

Rose, M.R., Long, A., Mueller, L., Rizza, C., Matsagas, K., Greer, L., Villeponteau, B., 2010. Evolutionary nutrigenomics. In: Fahy, G., West, M., Coles, L.S., Harris, S. (Eds.), The Future of Aging: Pathways to Human Life Extensions. Springer, London, pp. 357–366.

Rose, M.R., Mueller, L.D., Burke, M.K., 2011. New experiments for an undivided genetics. Genetics 188 (1), 1–10. http://dx.doi.org/10.1534/genetics.111.128900.

Rose, M.R., Flatt, T., Graves, J.L., Greer, L.F., Martinez, D.E., Matos, M., Shahrestani, P., 2012. What is aging? Frontiers in Genetics 3, 134. http://dx.doi.org/10.3389/fgene.2012.00134.

Rose, M.R., Rutledge, G.A., Phung, K.H., Phillips, M.A., Greer, L.F., Mueller, L.D., 2014. An evolutionary and genomic approach to challenges and opportunities for eliminating aging. Current Aging Science 7 (1), 54–59.

Rose, M.R., 1984. Laboratory evolution of postponed senescence in *Drosophila melanogaster*. Evolution 38 (5), 1004–1010. http://dx.doi.org/10.2307/2408434.

Rose, M.R., 1991. Evolutionary Biology of Aging. Oxford University Press, New York, NY, USA.

Russo, L., 2004. The Forgotten Revolution: How Science Was Born in 300 BC and Why It Had to Be Reborn (Silvio Levy, Trans.), second ed. Springer-Verlag, New York, NY.

Santer, M., 2009. Richard Bradley: a unified, living agent theory of the cause of infectious diseases of plants, animals, and humans in the first decades of the 18th century. Perspectives in Biology and Medicine 52 (4), 566–578.

Service, P.M., Hutchinson, E.W., MacKinley, M.D., Rose, M.R., 1985. Resistance to environmental stress in *Drosophila melanogaster* selected for postponed senescence. Physiological Zoology 58, 380–389.

Shahrestani, P., Leung, H.-T., Le, P.K., Pak, W.L., Tse, S., Ocorr, K., Huang, T., 2009. Heterozygous mutation of *Drosophila Opa1* causes the development of multiple organ abnormalities in an age-dependent and organ-specific manner. PLoS One 4 (8), e6867. http://dx.doi.org/10.1371/journal.pone.0006867.

Shanks, N., Pyles, R.A., 2007. Evolution and medicine: the long reach of "Dr. Darwin". Philosophy, Ethics, and Humanities in Medicine 2, 4. http://dx.doi.org/10.1186/1747-5341-2-4.

Siegel, R., 1968. Galen's System of Physiology and Medicine: An Analysis of His Doctrines and Observations on Bloodflow, Respiration, Tumors and Internal Diseases. Karger Publishers, New York, NY.

Siegel, R., 1970. Galen's System of Physiology and Medicine: Observations and Experiments on Vision, Hearing, Smell, Taste, Touch and Pain, and Their Historical Sources. Karger Publishers, New York, NY.

Siegel, R., 1973. Galen on Psychology, Psychopathology, and Function and Diseases of the Nervous System: An Analysis of His Doctrines, Observations, and Experiments. Karger Publishers, New York, NY.

Simões, P., Santos, J., Fragata, I., Mueller, L.D., Rose, M.R., Matos, M., 2008. How repeatable is adaptive evolution? The role of geographical origin and founder effects in laboratory adaptation. Evolution 62 (8), 1817–1829. http://dx.doi.org/10.1111/j.1558-5646.2008.00423.x.

Snow, J., 1855. On the Mode of Communication of Cholera. John Church, New Burlington Street, London, UK.

Stearns, S.C., Koella, J.C., 2007. Evolution in Health and Disease. Oxford University Press, Oxford, UK.

Swallow, J.G., Hayes, J.P., Koteja, P., Garland Jr., T., 2009. Selection experiments and experimental evolution of performance and physiology. In: Garland Jr., T., Rose, M.R. (Eds.), Experimental Evolution: Concepts, Methods, and Applications of Selection Experiments. University of California Press, Oakland, CA, pp. 301–351.

Talmage, D.W., 1957. Diversity of antibodies. Journal of Cellular Physiology. Supplement 50 (Suppl. 1), 229–246.

Tenaillon, O., Rodríguez-Verdugo, A., Gaut, R.L., McDonald, P., Bennett, A.F., Long, A.D., Gaut, B.S., 2012. The molecular diversity of adaptive convergence. Science 335 (6067), 457–461. http://dx.doi.org/10.1126/science.1212986.

The Huntington's Disease Collaborative Research Group, 1993. A novel gene containing a tri- nucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell 72 (6), 971–983.

Ullmann, A., 2007. Pasteur-Koch: distinctive ways of thinking about infectious diseases. Microbe 2 (8), 383–387.

Van Voorhies, W.A., Curtsinger, J.W., Rose, M.R., 2006. Do longevity mutants always show trade-offs? Experimental Gerontology 41 (10), 1055–1058. http://dx.doi.org/10.1016/j.exger.2006.05.006.

Wainwright, M., 2003. An alternative view of the early history of microbiology. Advances in Applied Microbiology 52, 333–355. http://dx.doi.org/10.1016/S0065-2164(03)01013-X.

Welcome Trust Case Control Consortium, 2007. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 447 (7145), 661–678.

World Health Organization, 2014. Mobile Phones Help People With Diabetes to Manage Fasting and Feasting During Ramadan. WHO. http://www.who.int/features/2014/mobile-phones-diabetes-ramadan/en/#.

Yang, J., Benyamin, B., McEvoy, B.P., Gordon, S., Henders, A.K., Nyholt, D.R., Madden, P.A., Heath, A.C., Martin, N.G., Montgomery, G.W., Goddard, M.E., Visscher, P.M., 2010. Common SNPs explain a large proportion of the heritability for human height. Nature Genetics 42, 565–569. http://dx.doi.org/10.1038/ng.608.

Zampieri, F., 2009. Medicine, evolution, and natural selection: an historical overview. The Quarterly Review of Biology 84 (4), 333–355.

Zuk, M., 2013. Paleofantasy: What Evolution Really Tells Us About Sex, Diet, and How We Live. W.W. Norton, New York, NY.

Chapter 43

The Impact of Modern Medicine on Human Evolution

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INTRODUCTION

The Meaning of "Modern Medicine"

To discuss this topic, it is necessary, first, to define "modern medicine." The term "modern," in this case, means "current" or "contemporary," that is, from 1946 up to present, and it is not to be confused with the meaning given by scholars in history, according to which the modern era started with the Renaissance. "Modern medicine" is characterized by a continuous technological development. Technology is the driving force of medical advancements in diagnosis, clinical, and surgical therapy, as shown by immunohistochemistry, medical imaging techniques, gene therapy (Friedmann and Roblin, 1972), stem cell therapy (Bubela et al., 2012), natural and artificial organs, and tissue transplants. It may be difficult, by consequence, to give a definition to a science that moves so fast. Modern medicine could completely change, tomorrow, by the discovery of a new revolutionary technology.

However, the *epistemological structure* of medicine is remaining stable from the second half of 19th century up to now. Since then, medicine has become a *positive science* based on the method of anatomo-clinical correlations. Giovanni Battista Morgagni (1682−1771), professor of anatomy at the University of Padua Medical School, Italy (1715−1771), was the first to demonstrate that clinical symptoms were correlated with anatomical substrates, founding *organ pathology*, which revolutionized also clinical diagnosis (Zampieri et al., 2014). Morgagni's revolution reached its climax during the following centuries, when pathology passed from organ to tissues (histopathology) and cells (cell pathology), now reaching the finest molecular architecture of the human body (molecular pathology). This pathology changed medical practice, promoting the development of clinical tools for detecting the internal states of the body during a patient's life and disease, as well as treatments focused on the material seats and causes of diseases. The first instrument was the stethoscope, introduced by the French physicians René Laennec (1781−1826), thanks to which he was able to establish that clinical symptoms of tuberculosis were caused by cavities ("tubercles") in the lungs. Some decades later, in 1882, the German bacteriologist Robert Koch (1843−1910) discovered the material cause of these cavities, that is, *Mycobacterium tuberculosis*, also known as Koch's *bacillus*.

The focus on organs, tissues, cells, and molecules favored the development of drugs, instruments, and procedures to give physicians access to internal parts of the body during the life of patients. Antisepsis and anesthesia gave surgery the means to extirpate pathological substrates of diseases. Stem cells are the new frontier by which medicine would like to replace a whole population of diseased cells with a healthy one in patient's bodies. Medicine is also trying to cure diseases caused by genetic mutations by directly or indirectly manipulating DNA itself. Moreover, the focus on material causes of diseases favored the discovery that many of them were caused by external factors, such as bacteria, viruses, and chemicals. Their knowledge gave an extraordinary impulse not only to therapeutic, but also to preventive medicine, hygiene, and prophylaxis.

This model has been so successful to remain unaltered up to now. Since after Morgagni's revolution, to understand a disease, physicians have to find its material cause, from outside or inside, where it is seated in the body, how it affects normal processes in organs, tissues, cells, or molecules, and how these processes clinically manifest.

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00043-0

It is easy to see that modern medicine focuses on factors also affecting human evolution, that is, material changes in physiology and morphology of organs, tissues, cells, and molecules. Medicine tries to restore only pathological changes, irrespectively from their heritability, while evolution comprehends any inherited change, but many pathological changes are inherited and could play a role in our evolution, both in shaping adaptations and in decreasing adaptations for given functions. Moreover, by curing any kind of disease and spreading the culture of health, medicine contributes to create the human niche that affects our biological evolution. Modern medicine has changed societies, increasing welfare and human life span: these effects also, by definition, have an impact on how humans evolve now, in the proximate and remote future. Even the external causes of diseases, ie, virus, bacteria, and chemicals are, at the same time, factors affecting our evolution. The relationship between humans, virus, and bacteria have been producing important coevolutionary changes since the beginning of human history. Humans continuously develop adaptive changes to chemical factors, such as food, water, air, and pollutants.

How Human Behavior Can Affect Human Evolution

Medicine is a specific human activity because its principal feature is curing sick individuals. From the antiquity, medicine was considered an "art," rather than a science, even when based on scientific method and data collected by other sciences. Thus, the conceptualization of the impact of modern medicine on human evolution is possible only with a theory explaining how human behaviors can affect biological evolution.

This is a significant issue for evolutionary biology, because during late 19th and early 20th centuries, many scientists were convinced that only Lamarckian mechanisms explained human evolution, which was considered a special domain where changes of behaviors and social uses, promoted by our intelligence, were the most powerful in shaping adaptive hereditary changes. The British psychologist William McDougall (1871−1938) was convinced, for instance, that a new adaptive behavior, cognitively acquired, could be transmitted through heredity, and designed some experiment to demonstrate this hypothesis (McDougall, 1927, 1930, 1933; Rhine and McDougall, 1930). He thought that if modifications of function and structure acquired by the individual organism in consequence of its efforts to adapt itself to its environment could be to some degree transmitted to its descendant, then it was possible to assign to the human mind an intelligible and leading role in the "drama" of evolution (McDougall, 1927). Nowadays, many scientists take the position against sociobiological theories when applied to humankind, even if they use other kinds of arguments. As it is well known, sociobiology tries to understand animals' behavior in terms of natural selection, on the hypothesis that behaviors are inherited traits (Wilson, 1975). The general criticism against sociobiology is that the models used to explain behaviors of social insects, births, or mammals, could be only partially applied to humankind, because men have a much more complex nervous system, and as such genes and hereditary mechanisms are less crucial in determining their behaviors (Cronin, 1993).

The first models, describing in Darwinian terms how a change of behavior could indirectly promote new inherited adaptations, was probably the so-called "Baldwin effect." The American psychologist James Mark Baldwin (1861−1934) formulated the theory according to which a spontaneous behavioral change in a subpopulation, which proves to be adaptive, creates a selective pressure by which any spontaneous mutation coding for part of this change will be immediately acquired by the genetic pool of the population. Accumulating mutations along the same line, a new stable adaptive trait could be shaped (Baldwin, 1896). This principle can be applied to humans, and its reception by evolutionary biologists was probably because it gave a particular importance to adaptive changes promoted by human cognitive behavior. Baldwin advanced that humans' social instinct might have originated by a change of behavior, which ultimately became, thanks to the fixation of mutations coding for this trait, part of our genetic pool (Baldwin, 1896). Baldwin stressed also the importance, in our species as well as in other mammals, of the instinct of imitation. For children, it is enough to imitate what they experience in context, to be able to acquire language and whatever they need to adapt to their environment. The development of more complex cultures has created a selective pressure that favored the fixation of a genetic attitude for imitation. The instinct of imitation overcomes the difficulties in acquiring languages, cultural, and social rules too complex for becoming inherited (Baldwin, 1896).

The evolution of lactase persistence in humans can be interpreted with this model, since it is a mutation which became fixed by the selective pressure given by animal domestication (Gerbault et al., 2011), and also antimicrobial resistance, as an effect of healthcare. The resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections is generically caused by the use and misuse of antimicrobial drugs because it accelerates the emergence of drug-resistant strains. This, in turn, could have the effect of stimulating the fixation of new mutations in humans, resulting in the overcoming of these new resistance strains, in a continuous host−parasite arms race (Nesse and Williams, 1994; see later).

Another interesting example combining Baldwin effect and developmental evolutionary biology (EvoDevo;

for EvoDevo, see later in this chapter), regards a study published in the 1930s on the relationship between installing air conditioning in the hospital and patients' health. Close air-conditioned space is a new environment created by man, which may produce a mismatch between evolved human constitution and the new environmental factor. Constantin Yaglou (1897–1960), professor of Industrial Hygiene at Harvard's School of Public Health between the 1930 and 1950s, studied the effects of Harvard's new air-conditioned nursery, from 1926 to 1929, compared with a previous period, from 1923 to 1925, when this innovation had yet to be made. He found, for instance, that premature infants were less able to stabilize their body temperatures than infants born at term, a characteristic exacerbated in the air-conditioned climate. Among premature infants, the ability to regulate temperature changed depending on birth weight. These and other significant findings were used for the development of incubators, now fully entered in daily clinical practice (Blackfan et al., 1933; Yaglou, 1938).

EvoDevo is actually focusing on phenotypic and developmental plasticity, of which the interaction between behavior and environment is a key component. Biologists have observed that little mutations in genes controlling the development of embryo and other phases of life could have wide evolutionary effects, such as the emergence of new adaptive characteristics. It is no more necessary to have new genes to code a new trait, but it is enough to differently regulate genes already existing (Beldade and Brakefield, 2002). The model states that developing mammals made a prediction of their future environment from cues received from the maternal environment. This prediction is effected by epigenetic alterations that change the expression of genes which then influence how the individual responds to later predicted challenges (Gluckman et al., 2008). This model explained better than a purely genetic one the differences in individual disease risks in spite of similar lifestyles and the same environment. The epigenetic effects, as new research indicates, may be transmitted across generations (Jablonka and Raz, 2009). Even if the cases studied by EvoDevo regard mainly changes in utero, there are also studies addressed to occurrences later in life. For instance, there are some indications that, across several generations, the mother's age of menarche can influence her daughter's menarche (Mishra et al., 2007). There are studies also about the period of childhood, in particular regarding the diet which can affect later health, these effects being hereditarily transmissible. EvoDevo, by consequence, gives another scientific explanation on how a change in human behavior can affect human evolution.

Finally, the "niche construction" model is another fundamental instrument to understand how an animal and human behavior can affect biological evolution (Odling-Smee, 2003). Being this is an all-embracing model for any gene–culture interaction, it might be supported that all the examples we shall present in this paper are ascribable to this conceptual framework. Organisms regularly modify local resource distributions, influencing both their ecosystems and the evolution of traits whose fitness depends on such alterable sources of natural selection in environments. The changes that organisms bring about in their own selective environments can be an important source of modified natural-selection pressures and can generate some unusual evolutionary outcomes. For example, niche construction can cause evolutionary inertia and momentum, it can lead to the fixation of otherwise deleterious alleles, it can support stable polymorphisms where none are expected, and it can eliminate what would otherwise be stable polymorphisms (Laland et al., 1999). "Ecosystem engineering" deeply characterizes current humans' ecology and this engineering regards not only material changes by human technology, but also and even more specifically cultural features that shape our environment. In humans, much niche construction is influenced by socially transmitted behavior. Human cultural variation, depending largely on differential social transmission of information through social learning, may result in cultural niche-constructing practices that modify the natural selection of some human genes. Offspring inherit not only genes, but also an ecological inheritance, in the form of modified local selective environments relative to genetic fitness. Inherited physical resources could refer to aspects of material culture, for example, nutritional resources or tools, created through hunter-gathering activity or farming. Many inherited niches obviously consist of both informatic and physical resources: for instance, farmed livestock and crops are not just nutritional resources, but also a source of public information concerning subsistence practices (Laland et al., 1999). An example for medicine is given by drug treatments to prevent diseases, which may relax genetic selection for disease resistance or susceptibility. At the same time, antibiotic use, favoring selection of resistant bacterial strains, can result in cultural selection for the avoidance of antibiotic use. This example is also notable as a case of interspecific niche construction, as the cultural and genetic evolution of antibiotic use and bacterial strains, respectively, modify the selective environments of one another (Kendal et al., 2011).

EUGENICS

Contemporary Eugenics

The impact of modern medicine on human evolution has been discussed, in the recent past up to now, under eugenics theories. Even if prejudices of natives against foreign populations, as well as controls of birth for

improving the quality of inhabitants, existed since the antiquity in many countries, eugenics *stricto sensu* was born with Francis Galton (1822–1911), who coined the term in 1883 (Galton, 1883), and remained popular up to World War II. The terrible outcomes of racial policies in Germany caused the abandonment of eugenics policies in Western countries after the war. However, eugenics concerns exist also among contemporary scientists. One of the most brilliant evolutionary biologists of the recent past, William Hamilton (1936–2000), raised eugenics questions several times during his career. He was convinced that almost all of the worries of the early eugenicists were well-founded in spite of the relative paucity of their evidence at the time, referring to the pioneers, such as Francis Galton and Karl Pearson (1857–1936), not the political demagogues who, during Galton's epoch, undertook actions without much consideration and controlling the data. Still a junior lecturer at the Imperial College of London, Hamilton suggested that evolutionary biology might have something to say about intergroup conflict, particularly on how different rates of population growth exacerbate tensions between groups. In 1998, invited at the Pontifical Academy of Sciences in Vatican, Hamilton spoke about how modern medicine was causing long-term deleterious changes in the genome and how these changes made desirable a program of eugenics and selective abortion. Of course, his lecture was not well received on that occasion (Haig, 2003).

Hamilton worries that modern medicine eliminates natural selection and our genome will accumulate more and more deleterious mutations, because without natural selection, or with a relaxed one, the accumulation of harmful mutation accelerates. He fears that our scientific and technological abilities to diagnose and repair these mutations is insufficient and he does not believe that future technologies will improve to such an extent that we will be able to correct all deleterious mutations and keep our genome healthy. One of the examples he returns to very frequently is the cesarean section. This medical practice, according to him, relaxes the action of natural selection on the width of the female pelvis favoring narrower hips, because a female with narrow hips may give birth to a female with a similar trait. In other words, by surviving, thanks to cesarean section, the affected female can continue to reproduce, thus spreading the narrow hips trait. Hamilton proposes that government should offer a state reward for a pledge by this kind of woman not to bear more children (Hamilton, 2001). Hamilton, however, thinks that the evolutionary process by which females are developing narrow hips is based on mate choice, when probably it is due by an evolutionary mother–offspring conflict. Babies determine when to be born, and the tightness of the birth passage possibly reflects the evolutionary brinkmanship of fetuses remaining in the safety of the womb until almost the last moment at which it is safe to emerge (Haig, 2003). Moreover, Hamilton's worry has a disquieting historical precedent: Agnes Bluhm (1862–1943), German female physician and eugenicist, feared that medical assistance at birth allowed women to survive and reproduce who would otherwise have been unable to give birth, contributing to an increased incidence of birth complications due to narrower birth passages (Proctor, 1988). German Jews were accused of promoting hospital birth and cesarean section, so the Nazi regime shifted assistance at birth from physicians to midwives (Proctor, 1988).

The Evolution of Sex, the second volume of Hamilton's collected papers, was almost ready to be published when the author died in March 2000 (Hamilton, 2001). One of the major goals of this 800-page work, consisting in republished papers and chapters, was to initiate a debate on subjects that he considered to have been treated as taboo, particularly eugenics (Haig, 2003). The main problem, according to Hamilton, is that modern medicine is actualizing a "dystopia" in which individuals carrying lethal genes, who will require medication all of the time, will be even more common in future populations. Hamilton expressed similar ideas when he reviewed *Dysgenic: Genetic Deterioration in Modern Population*, a book by Richard Lynn, Professor Emeritus of Psychology at the University of Ulster, UK (Lynn, 1996). A number of well-characterized genetic diseases are under at least a weak dysgenesis in the sense that we are medically curing them and thus allowing their recessives (and sometimes heterozygous conditions, too) a cessation of the counterselection through death or disability that formerly kept the genes at very low frequency (Hamilton, 2000). This is only a part of the dystopia. In fact, medicine not only keeps alive those who carry mutation for diseases already known, but it can keep alive those who carry deleterious alleles generated by new mutations. These mutations will quickly accumulate if not purged by selection (Hamilton, 2001; Haig, 2003), eventually becoming destabilizing for civilization itself (Hamilton, 1988, 1991, 2001). Hamilton was convinced that in two generations the damage being done by ante- and postnatal lifesaving efforts of modern medicine will be obvious to all and be a big talking point of science and politics (Hamilton, 2001). By consequence, he proposes not only to reinforce prenatal selection, but also to execute infanticide, where it would be necessary, a proposal found disturbing by many of his readers (Haig, 2003). For instance, he wrote, "If early signs of a coming severe handicap can be detected during that early postnatal period, I hold that the kindest thing for the family in which the defective child is to be dependent, and for the child itself, may well be to kill it" (Hamilton, 2001).

Other contemporary scholars share some of the Hamilton's worries about the increase in harmful mutations in our genome. However, Hamilton is more pessimistic than scientists, such as, for instance, Steve Jones and John

Maynard Smith, who think we can repair the known deleterious mutations by engineering the germ line or soma. Their opinions, at any case, prove they also believe that modern medicine causes an increase of harmful alleles' frequency rate.

Weaknesses of Eugenics Theories

The idea that medicine is causing a degeneration of human constitution is based on the assumption that medicine is keeping alive those who would otherwise have perished. However, this is a misconception, which results from thinking of natural selection as eliminating through mortality, rather than changing through differential reproductive success. That an individual survives or not in given circumstances is not determinant, because evolution is based on reproduction, not on survival. Very often, medicine keeps alive diseased individuals, such as babies affected by cardiovascular malformations, not long enough to give them the possibility to have children.

Another fundamental argument of eugenics is that humans do not shape any more adaptive changes, because in modern times both fit and unfit individuals survive. In this way, medicine causes a relaxation of natural selection and selective pressure, by which mutant nonfunctional or harmful alleles increase in frequency. Now, it could be said that Western medicine, which is the only approach having important results in letting survive genetically diseased individuals, is still practiced only in a small portion of the world. We shall eventually advance that selective mortality in the developing world is keeping the human gene pool healthy, while the Western world enjoys the benefits from its advanced medicine, but it is a disturbing way to treat the argument. Another perspective can be to focus only on the developing world, trying to understand how the introduction of Western medicine is relaxing natural selection, obtaining a "measure" of how much natural selection is affected by this practice. To have a real effect, medical care of patients with a genetic disease has to maintain the fitness of the cured patient equal to that of a healthy one. If the selective differential of fitness remains, at least in part, and the mutation rate stays low, the genetic disease will probably increase a little in frequency, but without affecting a major proportion of the population (Haig, 2003). Moreover, much depends on the effect of this mutation in the phenotype. Some mutation has little health cost, while others are so severe that even the most advanced medicine cannot do much. As David Haig points out: "Only mutations for which medical care causes a substantial increase in reproductive fitness are relevant to this question" (Haig, 2003). We think that these cases are still quite rare. Therefore, contrary to Hamilton, we think that the problem of deterioration of human genome, if it exists, is not urgent and eventually will never become serious.

Eugenics arguments, in particular the early ones, probably were based on a misunderstanding of the role of medical practice in the "epidemiological transition" which revolutionized Western societies in the 19th century (Omran, 1971). The shift from acute infectious diseases to death via chronic, noninfectious, degenerative diseases was a result of a higher standard of living and the introduction of medical and public health practices in high-income nations undergoing industrialization, such as England, France, and Germany. Antibiotics, vaccination, antisepsis surgery, and a better hygiene favored by medical campaigns were the main factors in this spectacular transition. Eugenics scientists thought that the spreading of unfit individuals, saved by medical care, *caused* degenerative chronic diseases. These individuals could live enough to procreate children who, in turn, diffused their inherited unfit genome, impoverishing the population genetic pool. In reality, these new diseases emerged because of an increase of lifespan. As more and more of the population reached advanced age, thanks to the reduced infection threat, a rise in chronic diseases that typically began later in life became evident. Nevertheless, diseases of later age affected individuals irrespective of their genetic constitution, not because their genome was degenerated as an indirect consequence of medical practice. Moreover, old individuals are no more relevant to natural selection, because they usually do not reproduce.

Concerning the question about the evolutionary rate of current human species, there is plenty of evidence that humans are still evolving (Zimmer, 2009) and even that the rate of evolutionary adaptive change is becoming faster (Flintoft, 2006). For recent times, we mean both the evolutionary scale, that is, millions of years, and human scale, that is, centuries. A study examining differences in gene expression in the liver among more than 1000 human genes and their orthologues from the chimpanzee, orangutan, and rhesus macaque, found 19 genes that are expressed at the same level in the three nonhumans primates, but at higher or lower levels in humans compared with these other species (Gilad et al., 2006). The genes examined, being under stabilizing selection, remained constant across the entire phylogeny (about 70 million years), probably because changes in gene regulation may be deleterious and hence influence disease susceptibility. In fact, genes associated with human cancer are slightly enriched and the expression levels of five genes of this study have been shown to be altered specifically in liver carcinoma (Gilad et al., 2006). This research shows that the function and regulation of transcription factors have been substantially modified in the human lineage by a rapid evolution.

One study, working with large sets of genetic data, found that the rate of evolution by natural selection in humans actually *accelerated* over the time, perhaps because of the global population growth and because, by colonizing the world and creating complex cultures, we have subjected ourselves to a wide variety of new selection pressures.

Using a 3.9 million haplotype map (HapMap) single nucleotide polymorphism (SNP) dataset, the research found that selection accelerated greatly during the last millennia, creating new adaptations in our species (Hawks et al., 2007). This research was based on the data of the International HapMap Consortium, which, studying the HapMap of the human genome, found around 1800 gene variations that have become common in the past 50,000 years (The International HapMap Consortium, 2005).

Another paper, searching for genes under natural selection in Africans, Europeans, and East Asians, found in each population some 200 genes showing signals of recent selection (from 10,000 to 6000 years ago), but without much overlap, suggesting that the populations on each continent were adapting to local challenges. It was done on 800,000 SNP in 309 unrelated individuals, mainly autosome, searching for loci where strong selection has driven new alleles up to intermediate frequency. The 200 variants identified have not yet reached fixation, this meaning that they have been very recently selected, and, having substantially different fitness, they must indicate loci that are the source of significant phenotypic variations, probably of medical relevance (Voight et al., 2006).

Lactase persistence in human adult is another clear example of recent adaptive evolution. This ability is genetically transmitted as a dominant trait and lactase persistence in a population correlates with that population's history of cattle domestication (Bersaglieri et al., 2004; Gluckman et al., 2009). As is well known, humans started to domesticate animals about 10,000 years ago, a period that in the evolutionary perspective is short.

Another characteristic showing a "neotenic" process is the age of the first menarche, which has been continuously decreasing from the beginning of the 20th century (McDowell et al., 2007). It is neotenic because girls became sexually mature while retaining juvenile physical characteristics. This process is commonly explained by sociocultural factors. Because girls have to develop a certain amount of body fat in order to menstruate, access to food affects age at menarche. The age of menarche has a hereditary basis and, by consequence, an important relationship with fitness. It is generally accepted that natural selection, on one hand, favors an early age of first menarche because this improves the probability to have more children, and from the other hand, this pressure is counterbalanced by the necessity for the mother to be mature enough to take care of her offspring. Natural selection, by consequence, will favor a plasticity in the age of first menarche according to the environment. For instance, prenatal adverse factors can accelerate sexual maturation, because the embryo, predicting the same circumstances in the future, tries to reproduce as soon as possible. On the contrary, adverse situations during childhood seem to induce the infant to postpone sexual maturity, looking for better conditions in the future (Gluckman et al., 2009).

A French-Canadian insular preindustrial population has been recently studied in relation to the age at first reproduction among women. In this population, under a non-Malthusian regime and in absence of birth control, evolutionary model predicts a change toward earlier first reproduction, given that the trait is correlated, in such a situation, with an increase of fitness. The study found that women giving birth to their first child in the 1930s were about 4 years younger than those who began to reproduce around 1800 (Milot et al., 2011).

Another study, which focused on current human evolutionary changes, has been carried on with the data provided by the Framingham Heart Study, an epidemiological study which has tracked the health of thousands of people in Framingham, Massachusetts, since 1948. 2238 women were analyzed, looking for traits correlated with having a higher number of children. Researchers found that women with low cholesterol, greater body weight, shorter height, lower blood pressure, older age at menopause, and earlier age at first child, had more children on average than women without these characteristics and that these traits, by consequence, are under positive selection (Byars et al., 2009).

The model "genes-culture coevolution" gives important examples of human evolution in the most recent period of our evolutionary history, because industrial and post-industrial societies are ecosystems in which cultural activity, in its widest sense, plays the main role. We are entering a new epidemiological transition. It is characterized by the continued prominence of chronic, noninfectious disease now augmented by the reemergence of infectious diseases. Many of these infections were once thought to be under control but are now antibiotic resistant because of massive use of antibiotics in hospitals and elsewhere, while a number of "new" diseases are rapidly emerging. It is characterized by another cultural factor, namely the transportation system, that in our globalized era results in rapid and extensive pathogen transmission (Harper and Armelagos, 2010).

Another eugenics idea is that medicine, keeping alive sick individuals, gave to them the chance to reproduce and spread the genetic constitution at the base of their pathologies. This idea, in turn, is based on the assumption that diseases having a genetic basis are traits detrimental for evolution. However, diseases are not necessarily negative characteristics in evolutionary terms. A new discipline, namely evolutionary medicine, shows on the contrary that natural selection is often responsible for the maintenance of traits *vulnerable* to diseases, because of a balance between costs and benefits, or because a disease symptom can be a defense, rather than a defect, such as fever, cough or diarrhea (Nesse and Williams, 1994; Zampieri, 2009).

Evolution and, in particular, natural selection, does not shape "perfect" adaptations as it was generically understood before (Nesse, 2005). Since the early 1960s, George Williams (1926–2010) argued that natural selection acts to maximize the mean reproductive performance regardless of the effect on long-term population heath, wellness, or survival (Williams, 1966). This idea is at the basis of evolutionary medicine, which considers humans, as well as all other organisms, "bundle of compromises" shaped by natural selection and other evolutionary processes, in which any trait, even the best one in terms of fitness, can hide structural or functional vulnerabilities for the individual who carries it (Nesse and Williams, 1994). This is because "Evolutionary processes revolve around selection for maintaining the reproductive fitness, not the health or lifespan" (Gluckman et al., 2009). The evolution of upright posture, for instance, has been an adaptive process, but it shaped, at the same time, anatomical and physiological changes that now leave humans vulnerable to lower back pain, slipped disks, hemorrhoids, obstetric difficulties and other health problems (Nesse and Williams, 1994). Even the human eye, which has been long since considered a perfect human "machine," is fundamentally composed of a defective architecture. Nerves and vessels penetrate the eyeball in a bundle and spread out along the interior surface, instead of penetrating from the outside as in the better-designed cephalopod eye. Full field of vertebrate vision need a tiny nystagmus, which minimizes the shadows cast by vessels and nerves on the retina, and brain processing mechanisms, which extract the visual signal from the nystagmus noise. Octopi need neither of these processes, nor to worry about retinal detachment (Nesse, 2005).

Any adaptation is the outcome of a compromise between costs and benefits of the trait. Biological adaptive structures and functions are vulnerable in some aspect or under given circumstances. With this model, eugenics became not only ethically but also scientifically unjustifiable, because there are no more "absolute positive" traits to be preserved and no more "absolute negative" ones to be eliminated. Even a group of genes causing a disease can be related with current (or past, or future) adaptive traits. In the case of a disease caused by a trait whose genes were adaptive in the faraway past of our species, deleting these genes could deprive our species of an instrument which could return to be useful in the future, eventually coopted for another use. This process frequently occurred in our evolutionary history, and it is studied under the issue of "exaptation" (Gould and Vrba, 1982). This issue answers to the ambiguity of the concept of adaptation, because it defines both the process and the product of the process. Adaptation does not take into consideration, in fact, that a trait currently adapted for a given function could have been shaped, during the past, for another function, or even without any particular function related to fitness. To avoid the failure to recognize these characteristics, Stephen Jay Gould (1941–2002) and Elisabeth Vrba proposed the concept of "exaptation" for traits evolved for their usages, or for no function at all, and later "coopted" for their current role (Gould and Vrba, 1982). Exaptation can be of two types: (1) functional shift, with the reuse by natural selection with previously different purposes; (2) functional cooptation from nonadaptation, when natural selection leads to a useful structure of a trait previously nonadaptive, like a side effect, a developmental constraint, a structural effect, or a random insertion. Skull sutures, for instance, originated as developmental constraints and then reused in mammals as an adaptation to delivery (Pievani and Serrelli, 2011). A further case of type 2 is a structure or function which is, at the same time, an adaptation at one level of evolution (genes, organisms, groups, populations, species) producing an exaptation at another (Gould and Vrba, 1982). The concept of exaptation represents the best solution to the criticism on Darwinian gradualism, which affirms that incipient stages of useful structures could not function as the perfected forms do, so they cannot be selected. On the contrary, according to the exaptation model, the incipient stage performs a different function, then it can be coopted for another function and, once this new function has taken place, it improves its utility by natural selection. Feathers, for instance, were shaped for thermoregulation and then coopted for flight. Once this new effect was added to the function of thermoregulation as an important source of fitness, feathers underwent a suite of secondary adaptations to enhance their utility in flight. Any coopted structure will probably not arise perfected for its new effect. It will therefore develop secondary adaptations for the new role (Gould and Vrba, 1982).

Organic structures and functions, being adaptations or exaptations, are far from perfect. They are continuously improving by cycles of adaptation and cooptation in relation to a changing environment. Eugenics, by consequence, is even more illogical, because it does not take into account that "imperfection" is the constitutive condition and state of organic life.

Another important advancement concerns the role of genes as the main "protagonists" of evolution. This topic is important because eugenics theories are almost totally based on a "genocentric" view of biological evolution. Current evolutionary biology and evolutionary medicine, on the contrary, are well aware that genetic information is only part of the story of evolution, because multiple intervening variables and social contingencies influence phenotypic expression, and these influences may be *more* or less important than genetic information (McGuire and Troisi, 1998). Epigenetic mechanisms, moreover, are becoming a central aspect for the understanding of gene-expression dynamic, showing that our phenotype is the result of an interaction between genes and environment

(cultural and physical) in which the two factors are equally important (Gluckman et al., 2009). A kind of nongenomic heritable modifications has been discovered, in particular related to disease risk, contributing to a full understanding of the mechanisms by which evolution shapes our traits and vulnerabilities. In particular, a field devoted to the developmental origins of health and disease (DOHaD) has emerged, which is focused on specific aspects of the broader biological mechanism of *plasticity* by which organisms, in response to cues such as nutrition or hormones, adapt their phenotype to environment. These responses may be divided into those in which fetus or child change its phenotype for immediate benefit and those aimed at prediction of a future environment: disease occurs in the mismatch between predicted and realized future. The likely mechanisms that enable plasticity involve epigenetic processes, affecting the expression of genes associated with regulatory pathways. There is evidence that epigenetic marks may be inherited and so might contribute to nongenomic heritable disease risk (Gluckman et al., 2010).

None of this means to leave the Darwinian foundation of current evolutionary biology, because natural selection among genes continues to play a fundamental role. Without DNA, also nongenomic modifications should not take place, because they change DNA expression along some generation. Similarly, without DNA, modifications in the human physico-cultural niche could not have an evolutionary impact.

THE IMPACT OF MODERN MEDICINE ON HUMAN EVOLUTION

Even if eugenic assumptions are mistaken, this does not mean that modern medicine does not have an impact on human evolution. On the contrary, medicine affects human evolution in many ways. It contributes to the human "niche construction," since it is a scientific practice that has an impact on both individuals and societies. It influences mortality rate, population's health and growth, and population's coevolution with biotic and abiotic environment (see later). Contrary to early and current eugenicists, we believe that these effects could not be categorized as always detrimental for the evolution of our species. Being understood that predicting long-term changes is very difficult, empirical evidences and theoretical models support the view that medicine affects human evolution sometimes favoring new adaptations and sometimes increasing harmful alleles' frequency rate.

Diagnostic Procedures

Genetic diagnosis can be applied on prenatal screening, eventually becoming a way to prevent the birth of child with genetic untreatable diseases. The first genetic disease to be diagnosed by this procedure was Huntington's disease in 1983 (McKusick, 2001). In this way, medicine should be seen as acting in favor, rather than against, natural selection, because it gives the opportunity to stop pregnancy and diffuse deleterious mutations. However, genetic screening is different from genetic testing or diagnosis, because the first assesses only the degree of risk that the fetus may potentially have certain common birth defects, but cannot tell with certainty if the baby actually has the problem. There is also the preconception genetic screening, when the test is done before pregnancy to determine whether the mother or father carry a gene for genetic disorders that might run in families, such as cystic fibrosis and sickle cell anemia, and could be passed on when the couple conceives. It is not a common practice, but it can surely prevent some couples to give birth to a child with high probability to have an untreatable disease.

While genetic screening is advancing, ethical concerns have grown about its use and consequences. The state of Pennsylvania in the United States promulgated the Down Syndrome Prenatal Education Act in 2014, also known as Chloe's Law, from Chloe Kondrich, an 11-year-old child who has Down syndrome. Chloe's dad was horrified to learn that the vast majority of mothers choose abortion if they learn their fetus is at risk for Down syndrome. He pushed the Pennsylvania state legislature to enact a law for better informing and supporting the future parents about Down syndrome, giving a positive view of the condition rather than a negative one (Caplan, 2015). This law overturns the long-standing foundational ethical norm of genetic testing and counseling, that is, *neutrality* in the provision of information. Genetic screening is developing faster and soon will be a standard procedure for every pregnant woman, not only for detecting Down syndrome, but also for many other diseases. By consequence, ethical concerns will become a fundamental issue, because parents will be eventually influenced by a disability-friendly normative message. It is difficult, at any case, that the change in genetic screening will affect human evolution. It will favor an increase of individuals affected by Down syndrome in the population, because more women will decide to continue the pregnancy, but without affecting the frequency rate of the chromosomal defect, because the disabled only very rarely could have a child.

Genetic diagnostic procedures can be applied also to diagnose diseases early, which before were detected too late for treatment. There is no cure for phenylketonuria (PKU), for instance, but newborns who are diagnosed early and maintain a diet low in phenylalanine (Phe) can have a normal life span with normal mental development. Women with PKU can have normal pregnancies when they maintain the low-Phe diet. With these new technologies, some PKU men have become fathers. In those cases, the mutation is transmitted to the next generation. Because of this

success, PKU has become increasingly common, but being a rare disease (1/10,000−15,000), the global effect would be negligible. Another interpretation is possible, given by the possibility that the heterozygous state could have a positive effect in carriers. A dated but interesting study found that heterozygosity for the PKU allele is advantageous in parents by rendering their unaffected offspring more viable at birth, thereby improving the chance of survival of the allele. Unaffected offspring of parents heterozygous for the PKU approaches the optimal birthweight, compared to Norwegian neonates, which confers the minimum overall mortality in pre-, peri-, and postnatal periods. This near-optimal birthweight, together with the possibly higher effective fertility observed in PKU heterozygous couples (at least in those who married in Norway before 1940), has apparently more than outweighed the disadvantages of the allele in PKU homozygous offspring as shown, for example, in an excessive number of pre- and perinatal deaths among the total offspring of PKU heterozygotes, to say nothing of the PKU survivors who, often, used to die young (Saugstad, 1977). In this case, if medicine keeps alive also homozygous children, it indirectly promotes a mutation being more frequently favorable than unfavorable.

The possibility to "diagnose" genetic defects specific for different ethnicity has been recently advanced by a so-called "racial medicine," particularly in the United States. While traditional clinical trials were once conducted mainly on white males, now in the United States most clinical trials, as well as large observational studies, take into account characteristics such as age, gender, and race/ethnicity. The 1993 National Institutes of Health (NIH) Revitalization Act required for all NIH-funded research involving human subjects to have as diverse a participant cohort as possible, unless there were strongly justifiable reasons to do otherwise (Norris, 2014). This approach revitalized the concept of race and pushed researchers to find different genetic disease susceptibilities according to ethnicity, even if this concept, unlike gender and age, has no consensus criteria for definition. Clearly, there are genetic predispositions with different rates in different populations, but this is not statistically enough to recover the notion of "race." As is well known, there is more genetic variation within these racial groups than across them. For instance, genetic diversity among the major continental populations is only 10−15% versus 85−90% within each continent. However, while race itself is not a biological variable, a group self-identifying as a given race may share biologic characteristics originated because of shared ancestry (Norris, 2014). Some African Americans, for instance, share with their ancestors two independent sequence variants in the *APOL1* gene on chromosome 22, which predispose them to higher rates of kidney disease than European Americans, who don't have these variants (Genovese et al., 2010). Based on this and similar studies, American health agencies are making race an important part of their policies, but from this assumption some scientists are trying once more to propose race as a biological entity (Leroi, 2005). To enter into that discussion is beyond the scope of this chapter; what we can advance is that medicine, considering these ethnic genetic differences among populations, seems to be (or should be) going not in the direction of a racial medicine, but in the direction of an even more "personalized medicine." A medicine which takes into account not just the ethnicity of a given patient, but his specific and unrepeatable past and recent history inside *also* his ethnical—and evolutionary—origin. This is also the aim of evolutionary medicine, which tries to take into consideration, thanks to evolutionary models, genetic and epigenetic individuality of single patients. Interindividual variations, at any case, is so high that medical care will never be able to permanently change frequency rates of alleles, affecting this diversity. For example, even if medicine manages to keep alive all American Africans who carry the variants in the *APOL1* gene on chromosome 22, these alleles will hardly diffuse to the global African populations, exactly because of their extreme genetic variability.

Irrespective of ethnicity, genetic diagnosis is becoming a clinical daily practice for many diseases and it is particularly effective for monogenetic ones and for those with few genes involved. For instance, a group of mutations involved in the arrhythmogenic right ventricular cardiomyopathy (ARVC), an inherited heart disease causing abnormal heart rhythm and eventually sudden death, has been identified (Thiene et al., 1988). The gold standard test is genetic diagnosis, and in case of a positive test, relatives are investigated to treat the disease and prevent sudden death (Thiene, 2015). However, ARVC is rare; in the United States its prevalence is approximately 1/10,000, even if studies found a prevalence of 1/200 of mutations predisposing to the disease (Lahiten et al., 2011). Because of its rarity, as in many other cases, medical care can eventually cause a little increase in frequency of these mutations, but without affecting the human genome as a whole.

Therapeutic Procedures

Acute Versus Chronic

The efficiency of medical treatments continually improves with new drugs, and clinical and surgical procedures, allows for more cures for diseases. In many cases, diseases that were previously acute or mortal are now chronic, such as HIV, cancer, diabetes, and multiple sclerosis, enlarging the lifespan of patients who would have died in previous centuries. One could advance that mortal or acute diseases

should act as selective pressures that favor evolutionary adaptive changes, improving the defenses against them, or by eliminating the weakest individuals. If they became chronic, selective pressure should fall down. When these diseases have a genetic basis, to change them in chronic could lead to an increase of the frequency of the harmful alleles among the population, because diseased individuals have more chances to reproduce. However, most of these diseases either do not have a genetic basis, such as infectious ones, or affect individual health after the reproductive period. Cancer, diabetes, and multiple sclerosis normally affect mature individuals. The little percentage of young affected either do not survive, or, if they do, they are a minority who cannot have an impact on the evolution of global population.

We could eventually advance that medicine, extending the lifespan of patients in the postreproductive period, might promote the fitness of their families, because some of these individuals will be grandparents contributing to the fitness of their grandchild, taking care of them together with their parents. One of the corollaries of "kin selection" theory, in fact, is that all the members of a family, taking care reciprocally, contribute to the fitness of shared genes (Hamilton, 1968). Now, if the genes predisposing to diabetes, for instance, runs in a family, medicine, curing some of its members, will contribute to their diffusion. This eventuality, however, is rare, because even inside a family there is great genetic variability from mother and father lineages. Moreover, the genetic variability generated by the marriages of children with individuals from other families may probably delete or dilute this tendency.

As in the case of infectious diseases (see later), also for the chronic ones there could be the phenomenon of resistance. If resistance, in the case of infection, is a trait acquired by germs, which became resistant to antibiotics, in chronic diseases the resistance is a physiological process affecting patients who became gradually tolerant to the drugs used for curing their diseases, such as cancer (Chisholm et al., 2015). It is a process of evolutionary interest because drug tolerance is an adaptive trait which, being genetically based, should have been shaped by natural selection. The usefulness of drugs tolerance seems obvious, even if these kinds of easy explanations can be often wrong in evolutionary biology. The gradual tolerance of the ingestion of new substances could have represented, in the past, a fundamental ability to acquire sources of nourishment, in particular in period of starvation, or to sustain other needs, such as physical activity. About 40,000 years ago, for instance, Australian aborigines were already using nicotine from two different indigenous sources: *Duboisia hopwoodii* and *Nicotiana gossel*. North and South Americans also used nicotine from their indigenous plants *Nicotiana tabacum* and *Nicotiana rustica* (Saah, 2005). The tolerance to that substance has been selected probably because nicotine served as a stimulant useful for the lifestyle of these populations. Primitive populations may have exploited substances that now are considered psychoactive drugs as substitutes for costly, nutritionally constrained endogenous neurotransmitters (Sullivan and Hagen, 2002).

Medical treatments do not have an impact on evolution, because the use of drugs eventually maintains this ability, rather than changing it in whatever way. At least, continuing this stimulation, medicine will improve our adaptability to tolerate foreign substances, acting in favor of natural selection. At any case, a deeper knowledge of the evolutionary origin of this human trait could be useful for medicine to better design its treatment programs.

Drugs and Vaccines for Infectious Diseases

Concerning infectious diseases, it is well known that the use of antibiotics causes a double effect. On the one hand, antibiotics have been one of the prominent conquests of Western medicine. Smallpox is the first human infectious disease eradicated worldwide, thanks to a vaccination campaign launched by the World Health Organization in the 1960s, declared successfully concluded on December 09, 1979 (Fenner et al., 1988). Leprosy, syphilis, tuberculosis, cholera, and other infectious diseases, killing millions of people in the past, now are curable and almost disappeared in developed countries. Antisepsis favored an extraordinary development of surgery, by which medicine cures serious injuries and noninfectious diseases, such as congenital malformations. The use of antibiotics, in sum, is one of the determinant factors of the exponential growth of global population during the last century, because of a dramatic reduction of mortality rate. Incidentally, this global growth can be interpreted as acting both in favor and against evolution of new adaptations in humans. A reduction of mortality rate could have lead harmful alleles to increase in frequency, but also could have given to natural selection a wider range of genetic variability from which to select new advantageous alleles. This extraordinary success led people to think that human's struggle against infectious diseases was over and that we will live, in a near future, completely free from any kind of harmful germ. Moreover, some evolutionary biologists in the past thought that the relationship host-parasite necessarily evolved, by natural selection, from an initial high virulence of the parasite to a final form of a mutualistic or commensalistic relation, in which the parasite, in exchange for resources given by the host, would not cause any harm (Dobzhansky, 1951). Unfortunately, the pandemic of HIV changed the mind of scientists, who suddenly faced the emergence of a new infectious disease with dramatic effects. Many of them get back to study the evolution of virulence, understanding that the relationship host-parasite only rarely reaches an equilibrium. The optimal virulence of a pathogen is determined

by a trade-off between maximizing the rate of transmission and maximizing the duration of infectivity (Anderson, 1982). Virulence can increase, by consequence, when germs find cultural or biological vectors, and/or when they can live also outside the host (Ewald, 1993). Natural selection will remove highly lethal pathogens if the host's death greatly reduces transmission, but if there is a vector which allows transmission, its death could even become the best strategy for the parasite. On the other hand, scientists are becoming more sensible about the evolution of resistance in bacteria, realizing that massive use of antibiotics inside and outside hospitals can favor this process by determining a high selective pressure which, combined with the high genetic variability of germs, have dramatic effects on reducing the efficacy of drugs. To treat dangerous *Staphylococcus* infections, for instance, with Penicillin (1946), we passed to Methicillin (1961), then to Vancomycin (1986), then to Zyvox (1999) (Palumbi, 2001), and this arms race is destined to continue. Bacteria, moreover, can rapidly acquire resistance by the phenomenon of conjugation, according to which collections of antibiotic genes are disseminated throughout an entire population of pathogens (Davies, 1995).

At least in some circumstances, indiscriminate vaccination campaigns can be more harmful than beneficial for populations because they select for the evolution of greater virulence, causing higher mortality among hosts (Boots, 2015). In particular, an "imperfect" vaccine that keeps alive the host but does not prevent transmission of germs will favor strains of bacteria that extend the infectious period at the point to be lethal for the host. A paper shows experimentally that immunization of chickens against Marek's disease enhances the fitness of more virulent strains, making it possible for hyperpathogenic strains to transmit (Read et al., 2015). A vaccination that "sterilizes" the host, preventing the infection of vaccinated individuals, represents a dead-end for parasites, but also in this case there is the possibility that a mutant bacteria would be immune to the host's defense. Fortunately, human vaccination programs have mostly been "sterilizing" up to now, but vaccination programs with "imperfect" vaccines are being implemented, thus representing this kind of threat (Boots, 2015).

Hospitals are probably where new multidrug-resistant (MDR) strains of bacteria are mostly favored, because of massive use of antibiotics, continuous circulations of people, and air conditioning, which contributes to the diffusion of germs. About 4.5% of patients admitted in US hospitals in 2002 were estimated to be affected by hospital-acquired infections (Peleg and Hooper, 2010). Most frequent and dangerous are the resistant gram-negative bacteria, such as *Escherichia coli*, *Salmonella enterica*, and *Klebsiella pneumoniae*. *Pseudonomas aeruginosa* has evolved from being a burn-wound infection into a major nosocomial threat, of considerable concern for patients with cystic fibrosis, because resistance development is associated with their lengthy antibiotic treatment (Davies and Davies, 2010). These and other gram-negative pathogens can survive outside the host, use medical staff and ventilators as vectors, and use some medical instruments and procedures to enter into the host (eg, the catheters), not to mention the approximate hygiene in some hospital contributing to this threat (Peleg and Hooper, 2010). Given the rapidity by which bacteria became resistant, pharmaceutical companies are investing even less money in research programs for new drugs, raising a big concern in national and international health care systems (Boucher et al., 2009)—a concern coupled with that of the continuous emerging of new resistant strains of parasites. For example, MDR *M. tuberculosis* is a major pathogen found in both developing and industrialized nations, being the 20th century version of an old pathogen (Davies and Davies, 2010).

Besides the vaccines, most of the treatments act by reducing the infectious period, being only "symptomatic." This reduction can both decrease and increase virulence of parasites, depending on other variables such as pathogens load within host, transmissibility of germs among hosts, contact rate and modalities among infected patients and susceptible individuals, and so on. In general, given that pathogen virulence evolves according to a trade-off between maximizing the number of new cases generated per unit time and maximizing the duration of infectivity, the reduction of duration by treatment may increase the virulence when it is proportionally related with transmission (Porco et al., 2005). The virulence of a germ often coincides with its load in the host, so that the more germs there are in a host, the more probability some of them have to be transmitted to other hosts. By consequence, a pathogen which cannot remain longer in its host reacts by increasing its virulence and transmissibility.

Medicine seems to act both in favor and against the evolution of adaptive changes in humans, according to its effects on the evolution of more or less virulent germs. However, to foretell an evolutionary effect, we should be in front of long-term changes, while these processes are, by definition, strictly related to contingency factors. The continuous arms race between humans and pathogens will almost surely remain stable in our evolutionary history, and medicine is and will be a powerful, but not determinant, tool to cope with the continuous genetic variability by which germs try to escape our defenses.

Genetic Therapies

In regards to genetic therapies, from the work of Victor McKusick (1921–2008), pioneer of American genetic medicine (Romeo, 2008), we dispose of an even more detailed "morbid anatomy of human genome" (McKusick and Amberger, 1993). Medical genetics is a frontier

discipline, given that molecular mapping of genes was possible not before the 1980s, and genetic therapies are under rapid development but they are not a real therapeutic option yet. McKusick was editor in chief of the *Mendelian Inheritance in Man*, published by the John Hopkins University Press until 1998, and father of the *Online Mendelian Inheritance in Man* (www.omim.org), which is still the most consulted genetic database in the world for human genes, genetic disorders, and traits, continuously updated up to now (McKusick, 2007).

McKusick defined genes as the "neo-Vesalian basis for medicine in the 21st century" (McKusick, 2001). Given that Andreas Vesalius (1514−1564) is the founder of modern human anatomy, this means that genes are the new frontier for the study of human health and disease. The linear arrangement of genes on our chromosomes forms our "microanatomy" and medical genetics has its specific "organ" of study, the "nucleus" of cells, as cardiology has the heart, neurology the nervous system, etc. (McKusck, 2001). These statements confirm what we have discussed in the Introduction of this chapter, that is to say that "modern medicine" is focused from macroscopical substrates of diseases to the finest molecular organization and it is, by consequence, predisposed to affect the evolution of our body.

Of the approximately 25,000 genes of human genome, mutations in more than 1800 have already been identified as causing hereditary disorders, but this does not imply we are able to correct these mutations in the human genetic pool (O'Connor and Crystal, 2006). First, we have to consider that there are different kinds of genetic diseases, the main two categories being dominant and recessive, even if they represent a simplification of a much more complex situation. In McKusick's *Mendelian Inheritance in Man*, in fact, a distinction between autosomal dominant and autosomal recessive traits has not been maintained since 1994. The reasons for discontinuing this distinction included the fact that entries were being created for an increasing number of genes for which there was extensive information, including location on a specific autosome, but no associated Mendelian phenotypic variation with either dominant or recessive inheritance. In addition, the distinction is only relative—that is, whether dominant or recessive sometimes depends on the level at which the phenotype is analyzed. Furthermore, there are rather numerous examples of particular phenotypes that are inherited as dominant or recessive based on different mutations in the same gene (McKusick, 2007). The concept itself of a monogenetic trait and monogenetic disease is an oversimplification, because the complexity of relationship between genotype and phenotype is maintained also in these cases, such as PKU (Scriver, 1999). For any genetic trait and disease, in fact, is valid based on the equation, $V_p = V_g + V_e$, Where "V" is variation, "p" is the phenotype, "g" the genotype, and "e" the environment (Speicher et al., 2010).

If the distinction between autosomal dominant and autosomal recessive is removed, it results that the effects of medical care are very difficult to verify and quantify in evolutionary terms. While if we maintain the distinction, the hypothetical effects seem to be low. For recessive genes, the number of people with the disease is vastly outnumbered by the number of carriers. Depending upon how rare the recessive allele is, there may be thousands or even millions of carriers for every person with homozygosis of the recessive allele. Removing the affected individuals from the breeding population will have an insignificant effect on the frequency of the recessive allele in the population (Novella, 2007). Moreover, some monogenetic diseases in recessive homozygosis seem to have an advantage in heterozygosis. This advantage, in terms of survival and reproduction, is believed to have been the cause of the maintenance of these alleles, throughout our evolutionary history, in high frequency. We have already mentioned the hypothetical advantage of the PKU; here we can mention sickle cell anemia and cystic fibrosis. The first disease is caused by genes that in heterozygosis give a protection against malaria and are found in higher frequency in the environment where this infection is endemic (Luzzatto, 2012). The second one gives protection, in an analogous way, against typhoid fever (Pier et al., 1998).

Dominant genetic diseases are different: every person carrying even one allele with the disease variant will have the disease. It should be further enquired how and when the disease manifests. If it manifests after the age at which most people have children, then it will not necessarily be selected against anyway, as in the case of Huntington's disease. If it manifests in childhood and is very severe, even fatal, despite modern medicine, then medicine will not be salvaging the disease allele. Nevertheless, if we can keep children with the dominant disease alive long enough to have children of their own, we will be increasing the frequency of the disease in the population. In such cases, people know they have the disease because everyone with the gene has the disease. This means that they can decide not to have children to avoid passing on their dominant gene (Novella, 2007). We have already mentioned the case of Down syndrome, so we can just reaffirm that ethical concerns will play an important role in preconception and prenatal genetic screening. In the case of monogenetic dominant disease, given there will be no doubt for the parents that their children will have the disease, to decide not to have a baby would be easier. Other more uncertain cases will represent very complex situations, both from an individual and a social point of view.

Spontaneous mutation rate is another fundamental element to take into account. All genetic diseases, in fact, have a spontaneous rate at which they renew in the population. Even if we removed all genetic diseases from the population, they would reappear again by mutation,

eventually reaching a steady state in the population. Improving the survivability may increase the frequency rate of these alleles, and by consequence the steady state of a genetic disease, but then genetic testing and counseling decreases its steady state. The latter effect may be greater than the former, which means that modern medicine may actually decrease genetic disorders, not increase them (Novella, 2007). When a genetic disease is diagnosed with more or less probability in the fetus, this would lead parents to decide to stop pregnancy. Or when prenatal counseling predicts that parents carrying harmful alleles will surely give birth to a diseased child, this would led parents not to initiate pregnancy. As already discussed, however, of fundamental importance will be the way in which institutions will give information about genetic screening. From an ethical and legal point of view, to constrain parents not to have children is unacceptable, even if they carry genetic disorders heritable by their child. By consequence, institutions should give the best information on these disorders, as parents will be able to make the best decision about their pregnancies, looking not only for their desires, but also for the wealth of their child and eventually also their grandchild. For instance, CHOICES is a Web-based multimedia education program on implementing informed reproductive plans for patients affected by sickle cell anemia or trait. This program proved to be effective in assisting reproductive health decision making in populations affected by these genetic defects (Gallo et al., 2015).

Finally, we have to consider the specific "ecology" of human species. What we know about evolutionary change suggests that genetic innovations are only likely to become fixed in small, isolated populations. Human populations are no more in that situation from the 20th century, because also isolated ones are now connected to the world by information networks and, more important from an evolutionary point of view, by the transports. It is even rarer that a population reject any kind of contact from outside, or that some of its members do not leave the place of origin or that foreign people do not came to live in the previous isolated place. If populations are not isolated, as we are now, crossbreeding makes it much less likely for potentially significant mutations to become established in the gene pool. However, this does not mean that human species are not evolving, because we have proof that this is not the case. A strict physical isolation doesn't exist anymore, but some kinds of cultural borders among populations continue to allow genetic changes to become more or less frequent and fixed, as seen for populations in different continents (Voight et al., 2006; Genovese et al., 2010; Norris, 2014). Moreover, we may advance that, in the future, humans would reach the form of a "global isolated population" because of continuous reciprocal exchanges among previously separated populations thorough the elimination of any border. This unprecedented situation should create new possibilities for natural selection to operate. As we can see, the human niche construction is deeply affecting our own evolution.

Going back to genetic medicine, the great challenge of current basic research is to create therapies centered on transferring genetic material to correct or compensate for an abnormal phenotype associated with a particular genotype. The genetic material can be of three different types: (1) Coding for a single gene, as in gene therapy, which replaces the mutated gene or which helps the body to fight a disease; (2) Fragments of coding sequences, as in RNA modification therapy, for inactivating, or "knocking out," a mutated gene that is functioning improperly; (3) Entire genome, as in somatic stem cells (SSCs) or embryonic stem cells (ESCs) therapy. These types of genetic material represent the three main categories and strategies of genetic medicine (O'Connor and Cristal, 2006). Until 2006, pluripotent stem cells could be obtained only from human embryos, but this procedure involved ethical concerns hard to solve. SSCs, even if they divide or self-renew indefinitely as ESCs, generate only the cells of the organ in which they are located, and this represents an important limit of their application. In 2007, the Japanese physician Shinya Yamanaka discovered a technique to induce human fibroblast to pluripotent stem cells, overcoming the ethical problem of obtaining this kind of cells from embryos (Takashashi et al., 2007). Gene therapy, by consequence, is becoming the target for even more diseases and syndromes.

For the moment, however, genetic medicine regards only monogenetic hereditary disorders, because it is actually impossible to modify the genes involved in nonmonogenetic diseases, also given that some of them could have important functions. In these cases, however, genetic medicine could play an important role to compensate or modify diseased organs. Examples include gene therapy to induce angiogenesis to bypass blocked coronary arteries, or stem cell therapies to regenerate cardiac myocytes to treat a failing myocardium (O'Connor and Crystal, 2006). Cancer, disease related to a complex series of multiple mutations, is another issue in which gene therapy is already used (Brenner et al., 2013).

These therapies do not affect the human genome because they do not delete or substitute mutations. If they became effective and routinely practiced, they could favor some change in the same way organ transplant could do (see later in this chapter). To be able to treat a diseased organ could cause a fall of selective pressure toward the organ, and eventually favor the frequency rate of harmful mutations. In fact, also those who have mutations for diseased organs will be able to reproduce, spreading their harmful alleles. However, this situation will represent the scenario predicted by optimistic eugenicists who think we will be able to repair the known deleterious mutations by engineering the soma (rather than the germ line), without negatively affecting our evolution.

In regards to monogenetic diseases, though relatively rare, they affect millions of people worldwide and are responsible for a heavy loss of life. The global prevalence of all single gene diseases at birth is approximately 10/1000. In Canada, monogenic diseases, taken together, may account for up to 40% of the work of hospital based pediatric practice (Scriver et al., 2001). Monogenetic disease can be treated with gene-transfer ex vivo, by removing, modifying, and replacing cell population; or in vivo, by administrating a vector (plasmid, retrovirus, or adenovirus) containing the therapeutic DNA, either directly to the organ or into blood vessels that feed the organ. Ex vivo strategy could have a positive impact on human evolution, only if the modification passes hereditary to next generations, otherwise it may favor an increase of frequency rate of harmful alleles. In vivo should be the best strategy from this point of view, because it represents the possibility to repair our genome even against the eventual accumulation of deleterious mutations due to medical care, as advanced by optimistic eugenicists. Of course, natural variability of our genome will continue to produce harmful mutations each generation, but thanks to this technique, we should able to delete them. Two different strategies are possible. When the disease is caused by an intracellular phenotype, the gene has to be transferred to the specific population of affected cells. When the phenotype results from a secreted protein, it does not matter to which cells or organ the gene is transferred, with the caveat that proteins must be appropriately posttranslationally modified and proteins' levels appropriately regulated. Unfortunately, both of them are still not available for humans (O'Connor and Cristal, 2006). Researchers must overcome many technical challenges before gene therapy will be a practical approach for treating disease. For example, scientists must find better ways to deliver genes and target them to particular cells. They must also ensure that new genes are precisely controlled by the body. Finally, they require circumventing immune defenses against the vectors that carry the new gene, given that vectors used are plasmid, adenovirus, retrovirus, or lentivirus. The immunosuppressive therapies can have an impact on quality of life or lifespan of patients, decreasing their positive effect in evolutionary terms. Moreover, only retrovirus and lentivirus vectors, at present, mediate permanent insertion into the genome, which means that they are the only ones able to have an evolutionary impact. Adenovirus vectors cause innate and acquired host responses against viral capsids and transgene products, which limit expression of the transgene to only a few weeks at the most (Fausther-Bovendo and Kobinger, 2014). While retrovirus, permanently inserting into host genome, carries the risk of insertional mutagenesis, and consequent development of neoplasm (Suerth et al., 2014).

In addition, for the numerous gene-therapies in use, based on RNA modification or stem cells, similar problems arise. According to the Gene Therapy Clinical Trial Databases (http://www.abedia.com/wiley/), provided by the "Journal of Gene Medicine," in 2014 only 130 approved gene-therapy trials worldwide toward treating monogenetic disorders have successfully directed. Hematopoietic stem cell transplantation, for instance, is the most diffuse SSC therapy for various inherited diseases, such as lysosomal storage disorders, immunodeficiencies, hemoglobinopathies, and leukodystrophies. As in any kind of organ transplant, it entails the risk related to the requirement for immunosuppression of the host (O'Connor and Cristal, 2006).

With RNA modification, genetic therapy is focusing not on genes, but on epigenesis, a basic mechanism in the differential expression of our genes according to changing environments. The recent development of epigenetics is affecting our understanding of genetics itself and, by consequence, of genetic medicine. The eventual target of a genetic therapy, in fact, is not structural DNA sequences, but regulatory ones. Interesting to note that current genetic medicine, as already mentioned, tries to modify genetic expression, with RNA fragment, to correct or compensate for an abnormal phenotype, because a method permanently changing DNA sequences still does not exist. The modification on gene expression made by medicine, however, does not have an impact on human evolution, because it is not heritable.

In sum, treating monogenetic diseases by modifying phenotypic expression, such as in RNA therapy, could favor the spread of harmful mutations because individuals affected can survive and reproduce. To treat them by "extirpating" the mutations, such as in gene therapy, could have a positive effect by eliminating a detrimental variation from the genetic pool any time it will emerge. Stem cell therapies represent another frontier that can have a positive effect only if stem cells are taken from the patient, otherwise immunological defenses have to be overcome at a detriment to patient health. The new technique for reprogramming SSCs in pluripotent ones seems to not represent a significant advancement in evolutionary terms, again because it depends on if these changes are transmitted to offspring.

Finally, we have to consider also the cost of these techniques. The broad application of gene therapy has been hampered by its lack of similarity to the traditional pharmaceutical model of drug development. Contrary to normal drugs, the cost of gene therapy remains high after approval, an effect compounded by stacked license fees for the many patents needed for the various intellectual properties of one product. Moreover, given that most genetic drugs are designed for the genetic specificity of single patients, each of them became an "orphan drug." These market issues can lead to an unaffordable pricing structure with little appeal to major pharmaceutical companies (Brenner et al., 2013). For

the moment, by consequence, the specificity of these therapies means that only a small subset of patients might be suited to treatment and the eventual evolutionary effect, either positive or negative, is very negligible, and probably will remain as such for a long time.

Organ Transplant

Since the discovery of cyclosporine in 1971 (first use in 1979), organ transplant gained an enormous success in the cure of irreversible organ pathologies. In regards to genetic diseases just discussed, it has been advanced that organ transplantation for a monogenetic hereditary disorder is the ultimate genetic medicine in that it involves replacing, along with the relevant SSCs and differentiated cells, the organ that is malfunctioning secondary to the abnormal phenotype (O'Connor and Crystal, 2006). However, one should be concerned because this procedure could have the effect to remove a selective pressure for the evolutionary improvement of a given organ. Can we say, for instance, that the vulnerability of the cardiovascular system to cholesterol due to modern diet, or of the respiratory system to modern pollution, or of the liver to modern poisons, will increment because of a selective pressure's relaxation? Can we say, moreover, that this technique allows surviving and reproducing individuals with poor genetic constitutions for these organs?

As in almost all the other cases discussed in this chapter, the answer could be neither yes nor no, because it depends on too many variables that could not be directly related to medicine or natural selection, and because of that, we cannot make long-term previsions. From the natural selection perspective, transplanted patients are, in many cases, in a postreproductive period, so their contribution to evolution could be low. Eventually they can favor a diffusion of their "poor" genetic constitution for a given organ or system among the population, but they can also represent an evolutionary advantage for their families, taking care of their grandchild, as mentioned discussing about kin selection. In many cases, moreover, even the highest selective pressure can do nothing for the improvement of a given organ, because of developmental, structural, or physiological constraints. Human coronaries probably will always be vulnerable to atherosclerosis because it is not possible for natural selection to shape bigger or more than two or three arteries on the heart, because these vessels are already well designed for heart blood supply in a physiological condition. Given that humans do not have cutaneous respiration, moreover, they need coronary vessels to deliver oxygen to myocardium (Liem et al., 2001). Natural selection could not redesign completely the human system of oxygen supply just "for saving" some individuals who died for cardiac stroke due to coronary arteries occlusion. Again, some genetic feature that predispose to atherosclerosis seems to have been positively selected during our evolutionary history. Higher serum cholesterol, for instance, may have been advantageous in the course of the rapid increase in human brain size during human evolution and for its role in steroid hormone synthesis (Ding and Kullo, 2009). Finally, atherosclerosis is a disease of aging, affecting individuals in a period almost completely beyond natural selection's work (Thomson, 2013).

Another aspect worth considering is that transplanted organs could represent, rather than a dead-end for natural selection, a new adaptive challenge for human bodies and their immunological system. They could favor an immune system able to recognize between harmful and beneficial "nonself" molecules, cells, and organs. Even the new frontier of artificial organs may represent such a challenge. Artificial knees and hip are part of the daily surgical practice. Brain-controlled robotic arms, as well as a permanent artificial heart, are becoming real and effective surgical options. As our bodies will be constrained to adapt to new external "artificial" environments, such as the absence of gravity in space, so too will our bodies be forced to adapt to new internal artificial parts.

Finally, we have to consider the economic costs of medical care. In modern societies, due to economic constraints, it is impossible to translate in practice the entire technical wherewithal of medicine. This limit, in some sense, solves *upstream* eugenics concerns. The translation depends also from any country's health care system. In Italy, where health care is free and guaranteed by constitutional law, there is the tendency to reduce the costs for treating chronic diseases of the old to gain more resources for the young. Transplantation is discouraged in cases of old patients. For a liver transplant, for instance, the limit is 65 years. Physicians and health politicians have to optimize resources that are even more limited. If on the one hand the improvement of medicine changes acute diseases in chronic diseases, on the other hand medicine is decreasing economic resources for dealing with chronic diseases, because these pathologies are often in the old rather than in the young. Medicine, is increasing the life expectancy of populations, but at the same time is facing a decline of economic resources for dealing with aging-associated diseases.

Iatrogenic Disruption of Adaptive Symptoms

Therapeutic procedures of ancient medicine were more harmful than healthy. For almost every kind of pathology, physicians practiced aggressive bloodletting and purgatives. In this way, we should advance, with a little bit of joking, that ancient medicine contributed to natural selection because only the strongest survived from diseases *and* medical care. Even if modern medicine is different, we may state that something similar continues to happen. Many disease

symptoms are adaptive defenses, in particular against pathogens and other kinds of environmental threats. Pain, nausea, cough, fever, vomiting, diarrhea, fatigue, and anxiety are ways by which the human body tries to react to these factors (Nesse and Williams, 1994). However, modern medicine often cures symptoms such as unpleasant complications by using symptomatic treatments. As illustrated by evolutionary medicine, to block these symptoms could slow down the process of healing (Nesse, 2001a). In this sense, we can support the idea that modern medicine determines an iatrogenic pressure against physiological process of healing. To be optimistic, we should say that it is indirectly favoring, by this pressure, the evolution of human defenses against pathogens less unpleasant for individuals.

Research supports that the so-called "multiple organ failure syndrome" could be an adaptive process. Sepsis and other critical illnesses produce a biphasic inflammatory, immune, hormonal, and metabolic response. The combination of severe inflammation and secondary changes in the endocrine profile diminish energy production, metabolic rate, and normal cellular processes, leading to multiple organ dysfunction. This perceived failure of organs might instead be a potentially protective mechanism, because reduced cellular metabolism could increase the chances of survival of cells, and thus organs, in the face of an overwhelming insult. The procedures of current emergency medicine seem not appropriate to sustain this adaptive mechanism, in particular in its later phase. For instance, attempts to stimulate metabolism—such as with glucose-insulin or thyroid hormones—might be appropriate as part of early management but could be potentially damaging if the organism has entered a phase of established multiorgan dysfunction in which cells have reduced their intracellular metabolism to improve their chances of survival (Singer et al., 2004).

Finally, Randolph Nesse, father of current evolutionary medicine, elaborated the concept of "Smoke detector principle" for describing many defensive mechanisms during pathological processes (Nesse, 2001b). Defenses, such as flight, cough, stress, and anxiety, should theoretically be expressed to a degree that is near the optimum level needed to protect against a given threat. Many defenses seem, however, to be expressed too readily or too intensely. This is because when the cost of expressing an all-or-none defense is low compared to the potential harm it protects against, the optimal system will express many false alarms. By consequence, even if diseases' symptoms sometimes are more harmful than beneficial, they have to be maintained and even reinforced by medical practice, otherwise medicine will act against a fundamental adaptive process of our physiology. The smoke detector principle is an essential foundation for making decisions about when drugs can be used safely to relieve suffering and block defenses (Nesse, 2001b). A better understanding of evolutionary history and evolutionary processes seems to be crucial, once again, for improving medical care and its impact on human evolution.

Public Health

Populations are healthier than in the past thanks to advances in medicine, which is promoting a significant enlargement of lifespan. While in the first half of the 18th century, European populations had a mean life expectancy of 30 years, value similar to that in prehistory, now it is about 80 years, and it seems to be continuously increasing. At the beginning of the 20th century lifespan increased because more children reached adulthood, while it was not until the second half of the century that mortality rates began to decline within the older ages. Research for more recent periods shows a surprising and continuing improvement in life expectancy among those aged 80 or above (Oeppen and Vaupel, 2002; Christensen et al., 2009).

A change in lifespan is, in itself, an evolutionary change, but it is even more significant because it is related to other characteristics; between them the most important, from an evolutionary point of view, is probably that humans tend to reproduce at a later age. By consequence, the average number of children per family is progressively diminishing, which, in turn, means that there is less variation in population and that natural selection has less material to act upon. At the same time, to reproduce at a later age implies also more genetic variability in germ cells (Paul and Robaire, 2009). Researchers have shown that the diversity in mutation rate of SNPs is dominated by the age of the father at conception of the child. The effect is an increase of about two mutations per year. An exponential model estimates paternal mutations doubling every 16.5 years (Kong et al., 2012). If this surplus of variation, on the one hand, causes a rise of frequency rate of harmful mutations, it represents, on the other hand, more opportunities for natural selection to select new adaptive alleles. Moreover, if the population becomes, on average, older than before, this could give to natural selection the opportunity to act more on the individuals in the post-reproductive period because they remain important in family economies, for instance, in terms of parental care of grandchildren, etc. The extension of aging in humans has surely a social and evolutionary impact which has to be carefully analyzed (Trevathan, 2007). Changes in developmental patterns, as already mentioned, have been fundamental in driving evolutionary changes of humans and other organisms in the past (Gluckman et al., 2009).

The diminution of the average number of children per family can have an impact on women's reproductive health because they have a greater number of menstrual cycles, which might be related to an increased risk of ovarian cancer. A study conducted on 410 women founds

that risk for death of ovarian cancer was higher among women with highest number of lifetime ovulatory cycles (LOC) compared with those having the fewest LOC. It found also that women whose age at menarche was <12 years had a higher risk of death compared with women whose menses began at ≥14 years (Robbins et al., 2009). These conclusions are reinforced by the fact that pregnancies seem to reduce risk of ovarian cancer by clearing transforming cells from the ovaries ("ovarian clearance") (Adami et al., 1994).

Another issue of reproductive health related to human evolution is the medical treatment of infertility. If infertility is caused by a genetic defect that can be transmitted to offspring, medical treatment could cause a rise in the frequency rate of this mutation. Another risk is that medical treatment of infertility gives the chance to reproduce at an even later age. Current socioeconomic conditions of occidental countries show an important change of the role of women in society. The majority of women now work, and they have even less time to devote to pregnancy and to cure offspring. By consequence, women tend to delay pregnancy more than before. This change can have an effect on women's health, as mentioned before, because it might be related to an increase on ovarian cancer and, in general, a late pregnancy is more difficult and risky than an earlier one (Dietl et al., 2015). A late pregnancy also can affect offspring health because it has more probabilities to produce unhealthy offspring.

The use of antibiotics and the vaccination campaigns have the positive effect to reduce the incidence of infectious diseases. At the same time, however, they could determine a strong selective pressure for germs to mutate, escape drugs, become more virulent, and use vectors. We have discussed this issue earlier.

The improvement of hygiene in population, supported from the second half of the 19th century by medicine, could have caused, paradoxically, health problems. The use of disinfection, if it decreases our exposure to germs and infections, could lead to a lack of important stressors for our immunological system. It seems that the many allergies which have become so common in modern populations are caused by an excessive hygiene that does not allow our immunological system a proper development. The anthropic extinction of microfauna, caused in particular by urbanization and pollution, has impoverished ecosystems and weakened the necessary training of the immune system. The "Hygiene hypothesis" states that we are in a state of evolved dependence on organisms with which we coevolved (and that had to be tolerated) as inducers of immunoregulatory circuits. These organisms ("Old Friends") are depleted from the modern urban environment, causing a rise in frequency of autoimmune diseases such as allergy, type 1 diabetes and multiple sclerosis (Okada et al., 2010; Rook, 2012). Again, the human niche construction promoted by medical practice is having a deep impact on how we are evolving.

CONCLUSION

Natural selection is always present and works when there are organisms who reproduce, sexually or not, with modifications between parents and offspring that could be mutations, DNA recombination, epigenetic, or phenotypic changes. Natural selection is the necessary consequence of these fundamental mechanisms which are the essence of reproduction itself. We do not see how humans could back out of that. Maybe in a future civilization of clones? Natural selection is also the consequence of human behaviors, in the sense that the changes that organisms bring about in their own environments can be an important source of modified natural-selection pressures. Medicine sometimes assists natural selection in shaping adaptations and sometimes it favors the rise of frequency rate of harmful mutations, as any other human activity, as shown by the niche construction model.

Modern medicine affects natural selection in different ways. From one side it can directly act upon genes, with genetic screening, genetic therapies (in the future), and with selective abortion. From the other, it could affect evolution by changing human behavior and human environment. The hospital, in particular, is a new niche, which did not exist in our evolutionary past, expressly designed for curing diseases. This new environment has been fundamental in decreasing the mortality rate of human populations and in expanding our life expectancy. At the same time, it favors the emergence of resistant strains of bacteria.

The creation of hospitals may have analogous effects to the creation of the first human residences during the transition from nomadism to sedentarism. These new niches have given the advantage to protect humans against predators and atmospheric agents. At the same time, they caused new health problems, related to the closeness among men and domestic animals, which favored the emergence of many modern zoonoses and related to the smoke of fires inside houses, used for warmth and cooking. The inspiration of this smoke seems related to atherosclerosis. A paper found atherosclerosis in 137 mummies from ca. 3100 BCE to the early 20th century. While modern lifestyles can accelerate the development of plaque on arteries, the prevalence of the disease across human history shows it may have a more basic connection to inflammation and aging. Inflammation in the arteries, in particular, was probably caused in ancient people by the continued inspiration of smoke from the fires installed inside ancient huts and primitive houses (Thomson, 2013).

Many modifications caused by medicine are related to new selective pressures that could drive genetic frequencies

by favoring or opposing the fixation of new mutations or combinations. We cannot say, however, that medicine has favored or opposed human adaptive evolution in an absolute sense. When acting upon genes, in fact, only rarely would we have a net effect, positive or negative. Monogenic diseases are relatively rare, while in the case of polygenic diseases we cannot predict if the elimination of one gene would be healthier or harmful. When acting upon behavior or environment, the effects could be very different according to many factors. We can say, for instance, that a learned behavior that improves fitness also prevents genetic adaptation, which could be interpreted as a potential depletion of genetic heritage, but if this behavior or its learning gain a hereditary basis, there would be an enrichment of our genetic program.

We can safely say that modern medicine has not eliminated natural selection, for there is still plenty of individual variation in reproductive success in modern human populations. During the last 40,000 years, selection in humans has accelerated with a large amount of recent positive selection. This acceleration was mainly caused by the larger size and lesser reproductive isolation of the current human population, allowing for a higher probability that a potentially advantageous mutation could occur and, in some area, persist.

There is no reason to think that natural selection has been eliminated among humans, because miscarriage or spontaneous abortion, habitual abortion, stillbirth, premature birth, maternal death, and incurable infertility are examples of this mechanism in humans. Further examples are childhood deaths, infectious diseases (HIV, influenza, measles, EHEC, Ebola), and many incurable genetic diseases. When looking globally, infectious diseases are the number one killer of humans and therefore the main selective pressure exerted on our species. The H2N2 flu virus killed 70,000 people in 1957 in the United States alone. SNPs in a number of genes governing immunity affect a person's susceptibility to infectious diseases, and how sick he or she becomes from those infections. This creates an opportunity for natural selection (Novella, 2007).

Another important issue to underline is that modern medicine has probably affected human evolution very little until now and that's because, first of all, evolution occurs very slowly and most of the things that modern medicine have accomplished really affect people's lives when they have finished reproducing. Most people are having kids between the ages of 20 and 40 and this is a very healthy population, so most of those people do not really get the benefit of modern medicine.

Ethics and economy, finally, constitute further elements that constrain and contextualize the impact of modern medicine on human evolution. Not everything we would think theoretically justifiable or technically feasible could be done, either because it is not morally desirable or because it is not economically sustainable.

Given that medicine, as any other human activity, is related to human evolution, medical sciences should be well informed about evolutionary theory and processes. Evolutionary biology can be fundamental for disease control and suggests that it may therefore have an important role to play in the design of medical intervention both inside and outside hospitals. Evolutionary biology gives theoretical and experimental models by which it is possible to predict, given specific circumstances, the evolution of virulence in relationship to vaccinations or treatments. Medicine, using these models, can avoid a detrimental impact on the evolution of virulence and, by consequence, on human evolution. Evolutionary biology gives new insight about the nature of our body, our reactions, and symptoms against diseases. It is fundamental, by consequence, for making decisions about when drugs can be used safely. All of that represents further reasons to support the development of evolutionary medicine and its use as a basic science for all medical sciences.

REFERENCES

Adami, H., Hsieh, C., Lambe, M., Trichopoulos, D., Leon, D., et al., 1994. Parity, age at first childbirth, and the risk of ovarian cancer. Lancet 344, 1250–1254.

Anderson, R.M., May, R.M., 1982. Coevolution of host and parasites. Parasitology 85, 411–426.

Baldwin, J.M., 1896. A new factor in evolution. American Naturalist 30, 441–451.

Beldade, P., Brakefield, P.M., 2002. The Genetics and Evo-Devo of butterfly wing patterns. Nature 442, 442–452.

Bersaglieri, T., Sabeti, P.C., Patterson, N., Vanderploeg, T., Schaffner, S.F., et al., 2004. Genetic signatures of strong recent positive selection at the lactase gene. American Journal of Human Genetics 74, 1111–1120.

Byars, S.G., Ewbank, D., Diddahally, R., Govindaraju, R., Stearns, S.C., 2009. Natural selection in a contemporary human population. Proceedings of the National Academy of Sciences of the United States of America 107, 1787–1792.

Blackfan, K.D., Yaglou, C.P., Wyman, K.M., 1933. The premature infant: a study of the effects of atmospheric conditions on growth and on development. American Journal of Diseases of Children 46, 1175–1236.

Boots, M., 2015. The need for evolutionarily rational disease interventions: vaccination can select for higher virulence. PloS Biology 13, e1002236.

Boucher, H.W., Talbot, G.H., Bradley, J.S., Edwards, J.E., Gilbert, D., et al., 2009. Bad bugs, no drugs: No ESKAPE! an update from the Infectious Diseases Society of America. Clinical Infectious Diseases 48, 1–12.

Brenner, M.K., Gottschalk, S., Leen, A.M., Vera, J.F., 2013. Is cancer gene therapy an empty suit? Lancet Oncology 14, e447–e456.

Bubela, T., Li, M.D., Hafez, M., Bieber, M., Atkins, H., 2012. Is belief larger than fact: expectations, optimism and reality for translational stem cell research. BMC Medicine 10, 133.

Caplan, A.L., 2015. Chloe's law: a powerful legislative movement challenging a core ethical norm of genetic testing. PloS Biology 13, e100221.

Chisholm, R.H., Lorenzi, T., Lorz, A., Larsen, A.K., de Almeida, L.N., et al., 2015. Emerge of drug tolerance in cancer cell populations: an evolutionary outcome of selection, nongenetic instability, and stress-induced adaptation. Cancer Research 75, 930–939.

Christensen, K., Doblhammer, G., Rau, R., Vaupel, J.W., 2009. Aging populations: the challenges ahead. Lancet 374, 1196–1208.

Cronin, H., 1993. The Ant and the Peacock: Altruism and Sexual Selection from Darwin to Today. Press Syndicate of the University of Cambridge, Cambridge.

Davies, J., 1995. Vicious circles: looking back on resistance plasmids. Genetics 139, 1464–1468.

Davies, J., Davies, D., 2010. Origins and evolution of antibiotics resistance. Microbiology and Molecular Biology Reviews 74, 417–433.

Dietl, A., Cupisti, S., Beckmann, M.W., Schwab, M., Zollner, U., 2015. Pregnancy and obstetrical outcomes in women over 40 years of age. Geburtshilfe Frauenheilkd 75, 827–832.

Ding, K., Kullo, I.J., 2009. Evolutionary genetics of coronary heart disease. Circulation 119, 459–467.

Dobzhansky, T., 1951. Genetics and the Origins of the Species. Columbia University Press, New York.

Ewald, P.W., 1993. Evolution of Infectious Disease. Oxford University Press, New York.

Fausther-Bovendo, H., Kobinger, G.P., 2014. Pre-existing immunity against Ad vectors: humoral, cellular, and innate response, what's important? Human Vaccines & Immunotherapeutics 10, 2875–2884.

Fenner, F., Henderson, D.A., Arita, I., Jezek, Z., Landy, I.D. (Eds.), 1988. Smallpox and Its Eradication. World Health Organization, Geneva.

Flintoft, L., 2006. Following the signposts of selection. Nature Reviews Genetics 7, 246.

Friedmann, T., Roblin, R., 1972. Gene therapy for human genetic disease? Science 175, 949–955.

Gallo, A.M., Wilkie, D.J., Yao, Y., Molokie, R.E., Stahl, C., et al., 2016. Reproductive health CHOICES for young adults with sickle cell disease or trait: randomized controlled trial outcomes over two years. Journal of Genetic Counseling 25, 325–326 [Epub ahead of print].

Galton, F., 1883. Inquiries into Human Faculty and Its Development. Macmillan and Co., London.

Genovese, G., Friedman, D.J., Ross, M.D., Lecordier, L., Uzureau, P., et al., 2010. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science 329, 841–845.

Gerbault, P., Liebert, A., Itan, Y., Powell, A., Currat, M., et al., 2011. Evolution of lactase persistence: an example of human niche construction. Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences 366, 863–877.

Gilad, Y., Oshlack, A., Smyth, G.K., Speed, T.S., White, K.P., 2006. Expression profiling in primates reveals a rapid evolution of human transcription factors. Nature 440, 242–245.

Gluckman, P.D., Beedle, A., Hanson, M., 2009. Principles of Evolutionary Medicine. Oxford University Press, New York.

Gluckman, P.D., Hanson, M.A., Cooper, C., Thornburg, K.L., 2008. Effect of in utero and early-life conditions on adult health and disease. New England Journal of Medicine 359, 61–73.

Gluckman, P.D., Hanson, M.A., Buklijas, T., 2010. A conceptual framework for the developmental origins of health and disease. Journal of Developmental Origins of Health and Disease 1, 6–18.

Gould, S.J., Vrba, E.S., 1982. Exaptation – a missing term in the science of form. Paleobiology 8, 4–15.

Hawks, J., Wang, E.T., Cochran, G.M., Harpending, H.C., Moyzis, R.K., 2007. Recent acceleration of human adaptive evolution. Proceedings of the National Academy of Sciences of the United States of America 104, 20753–20758.

Haig, D., 2003. The science that dare not speak its name. Quarterly Review of Biology 78, 327–335.

Hamilton, W.D., 1968. The genetical evolution of social behaviour. Journal of Theoretical Biology 7, 1–16, 17–52.

Hamilton, W.D., 1988. Sex and disease. In: Stevens, G., Bellig, R. (Eds.), Evolution of Sex. Harper and Rowe, San Francisco, pp. 175–180.

Hamilton, W.D., 1991. Seething genetics of health and the evolution of sex. In: Osawa, T., Honjo, T. (Eds.), Evolution of Life. Fossils, Molecules, and Culture. Springer, Berlin, pp. 229–251.

Hamilton, W.D., 2000. A review of dysgenics: genetic deterioration in modern populations. Annals of Human Genetics 64, 363–374.

Hamilton, W.D., 2001. Narrow roads of gene land: the collected papers of W. D. Hamilton. In: The Evolution of Sex, vol. 2. Oxford University Press, New York.

Harper, K., Armelagos, G., 2010. The changing disease-scape in the third epidemiological transition. International Journal of Environmental Research and Public Health 7, 675–697.

Jablonka, E., Raz, G., 2009. Transgenerational epigenetic inheritance: prevalence, mechanisms, and implications for the study of heredity and evolution. Quarterly Review of Biology 84, 131–176.

Kendal, J., Tehrani, J.J., Odling-Smee, J., 2011. Human niche construction in interdisciplinary focus. Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences 366, 785–792.

Kong, A., Frigge, M.L., Masson, G., Besenbacher, S., Sulem, P., et al., 2012. Rate of de novo mutations and the importance of father's age to disease risk. Nature 488, 471–475.

Laland, K.N., Odling-Smee, J.F., Feldman, M.W., 1999. Evolutionary consequences of niche construction and their implications for ecology. Proceedings of the National Academy of Sciences of the United States of America 96, 10242–10247.

Lahtinen, A.M., Lehtonen, E., Marjamaa, A., Kaartinen, M., Heliö, T., et al., 2011. Population-prevalent desmosomal mutations predisposing to arrhythmogenic right ventricular cardiomyopathy. Heart Rhythm 8, 1214–1220.

Leroi, A.M., March 14, 2005. A family tree in every gene. The New York Times.

Liem, K.F., Bemis, W.E., Walker, W.F., Grande, L., 2001. Functional Anatomy of the Vertebrates: An Evolutionary Approach. Harcourt College Publishers, Orlando.

Luzzatto, L., 2012. Sickle cell anemia and malaria. Mediterranean Journal of Hematology and Infectious Diseases 4, e2012065.

Lynn, R., 1996. Dysgenic: Genetic Deterioration in Modern Population. Praeger, Westport & London.

McDougall, W., 1927. An experiment for the testing of the hypothesis of Lamarck. British Journal of Psychology 17, 267–275.

McDougall, W., 1930. Second report on a Lamarckian experiment. British Journal of Psychology 20, 201–215.

McDougall, W., 1933. Fourth report on a Lamarckian experiment. British Journal of Psychology 28, 321–333.

McDowell, M.A., Brody, D.J., Hughes, J.P., 2007. Has age at menarche changed? results from the National Health and Nutrition Examination Survey (NHANES) 1999–2004. Journal of Adolescent Health 40, 227–231.

McGuire, M., Troisi, A., 1998. Darwinian Psychiatry. Oxford University Press, New York.

McKusick, V., 2001. The anatomy of the human genome. A neo-Vesalian basis for medicine in the 21st century. Journal of the American Medical Association 286, 2289–2295.

McKusick, V., 2007. Mendelian inheritance in man and its online version, OMIM. Journal of Medical Genetics 80, 588–604.

McKusick, V., Amberger, J.S., 1993. The morbid anatomy of the human genome: chromosomal location of mutations causing disease. Journal of Medical Genetics 30, 1–26.

Milot, E., Mayer, F.M., Nussey, D.H., Boisvert, M., Pelletier, F., Réale, D., 2011. Evidence for evolution in response to natural selection in a contemporary human population. PNAS 108, 17040–17045.

Mishra, G., Hardy, R., Kuh, D., 2007. Are the effects of risk factors for timing of menopause modified by age? Results from a British birth cohort study. Menopause 14, 717–724.

Nesse, R.M., 2001a. How is Darwinian medicine useful? Western Journal of Medicine 174, 358–360.

Nesse, R.M., 2001b. The smoke detector principle. Natural selection and the regulation of defensive responses. Annals of the New York Academy of Sciences 935, 75–85.

Nesse, R.M., 2005. Maladaptation and natural selection. Quarterly Review of Biology 80, 62–71.

Nesse, R.M., Williams, G.C., 1994. Why We Get Sick? The New Science of Darwinian Medicine. Time Books, New York.

Norris, K., February 01, 2014. On race and medicine. The Scientist. http://www.the-scientist.com/?articles.view/articleNo/38950/title/On-Race-and-Medicine/.

Novella, S., May 07, 2007. Modern Medicine and Evolution. www.theness.com/neurologicablog.com.

O'Connor, T.P., Crystal, R.G., 2006. Genetic medicine: treatment strategies for hereditary disorders. Nature 7, 261–276.

Odling-Smee, F.J., 2003. Niche Construction. Princeton University Press, Princeton, NJ.

Oeppen, J., Vaupel, J.W., 2002. Broken limits to life expectancy. Science 296, 1029–1031.

Okada, H., Kuhn, C., Feillet, H., Bach, J.-F., 2010. The 'hygiene hypothesis' for autoimmune and allergic diseases: an update. Clinical & Experimental Immunology 160, 1–9.

Omran, A.R., 1971. The epidemiologic transition: a theory of the epidemiology of population change. Milbank Quarterly 49, 509–538.

Palumbi, S.T., 2001. Humans as the world's greatest evolutionary force. Science 293, 1786–1790.

Paul, C., Robaire, B., 2009. Ageing of the male germ line. Nature Reviews Urology 10, 227–234.

Peleg, A.Y., Hooper, D.C., 2010. Hospital-acquired infections due to gram-negative bacteria. New England Journal of Medicine 362, 1804–1813.

Pier, G.B., Grout, M., Zaidi, T., Meluleni, G., Mueschenborn, S.S., et al., 1998. *Salmonella typhi* uses CFTR to enter intestinal epithelial cells. Nature 393, 79–82.

Pievani, T., Serrelli, E., 2011. Exaptation in Human evolution: how to test adaptive vs exaptive evolutionary hypotheses. Journal of Anthropological Sciences 89, 9–23.

Porco, T.C., Lloyd Smith, J.O., Gross, K.L., Galvani, A.P., 2005. The effect of treatment on pathogen virulence. Journal of Theoretical Biology 233, 91–102.

Proctor, R.N., 1988. Racial Hygiene: Medicine under the Nazis. Harvard University Press, Cambridge, MA.

Read, A.F., Baigent, S.J., Powers, C., Kgosana, L.B., Blackwell, L., et al., 2015. Imperfect vaccination can enhance the transmission of highly virulent pathogens. PloS Biology 13, e1002198.

Rhine, J.B., McDougall, W., 1930. Third report on a Lamarckian experiment. British Journal of Psychology 24, 213–226.

Robbins, C.L., Whiteman, M.K., Hillis, S.D., Curtis, K.M., McDonald, J.A., et al., 2009. Influence of reproductive factors on mortality after epithelial ovarian cancer diagnosis. Cancer Epidemiology, Biomarkers & Prevention 18, 2035–2041.

Romeo, G., 2008. Victor McKusick, 1921–2008: the founder of medical genetics as we know it. European Journal of Human Genetics 16, 1161–1163.

Rook, G.A., 2012. Hygiene hypothesis and autoimmune disease. Clinical Reviews in Allergy & Immunology 42, 5–15.

Saah, T., 2005. The evolutionary origins and significance of drug addiction. Harm Reduction Journal 2, 8.

Saugstad, L.F., 1977. Heterozygote advantage for the phenylketonuria allele. Journal of Medical Genetics 14, 20–24.

Scriver, C.R., Waters, P.J., 1999. Monogenetic traits are not simple. Lessons from phenylketonuria. Trends in Genetics 15, 267–272.

Scriver, C.R., Beaudet, A.L., Sly, W.S., Valle, D., Childs, B., et al., 2001. The Metabolic and Molecular Bases of Inherited Diseases, eighth ed. McGraw-Hill, New York.

Singer, M., De Santis, V., Vitale, D., Jeffcoate, W., 2004. Multiorgan failure is an adaptive, endocrine-mediated, metabolic response to overwhelming systemic inflammation. Lancet 364, 545–548.

Speicher, M., Antonarakis, S.E., Motulsky, A.G. (Eds.), 2010. Vogel and Motulsky's Human Genetics. Problems and Approaches. Springer-Verlag, Berlin.

Suerth, J.D., Labenski, V., Schambach, A., 2014. Alpharetroviral vectors: from a cancer-causing agent to a useful tool for human gene therapy. Viruses 6, 4811–4838.

Sullivan, R.J., Hagen, E.H., 2002. Psychotropic substance-seeking: evolutionary pathology or adaptation? Addiction 97, 389–400.

Takahashi, K., Tanabe, K., Ohnuki, M., Narita, M., Ichisaka, T., 2007. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 131, 861–872.

The International HapMap Consortium, 2005. A haplotype map of the human genome. Nature 437, 1299–1320.

Thiene, G., Nava, A., Corrado, D., Rossi, L., Pennelli, N., 1988. Right ventricular cardiomyopathy and sudden death in young people. New England Journal of Medicine 318, 129–133.

Thiene, G., 2015. The research venture in arrhythmogenic right ventricular cardiomyopathy: a paradigm of translational medicine. European Heart Journal 36, 837–846.

Thomson, R.C., 2013. Atherosclerosis across 4000 years of human history: the Horus study of four ancient populations. Lancet 381, 1211–1212.

Trevathan, W., 2007. Evolutionary medicine. Annual Review of Anthropology 36, 139–154.

Voight, B.F., Kundaravalli, S., Wen, X., Pritchard, J.K., 2006. A map of recent positive selection in the human genome. Plos Biology 4, 446–458.

Williams, G.C., 1966. Adaptation and Natural Selection. Princeton University Press, Princeton, NJ.

Wilson, E.O., 1975. Sociobiology: The New Synthesis. Harvard University Press, Cambridge, MA.

Yaglou, C.P., 1938. Hospital air conditioning. Journal of the American Medical Association 110, 2003–2009.

Zampieri, F., 2009. Medicine, evolution and natural selection: an historical overview. Quarterly Review of Biology 84, 333–335.

Zampieri, F., Zanatta, A., Thiene, G., 2014. An etymological "autopsy" of Morgagni's title: De sedibus et causis morborum per anatomen indagatis (1761). Human Pathology 45, 12–16.

Zimmer, C., 2009. The origin of tomorrow. Science 326, 1334–1336.

Chapter 44

Science and Technology in Human Societies: From Tool Making to Technology

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TOOL MAKING

The adaptive strategies of all taxa belonging to the genus *Homo* included the use of stone tools, although the characteristics of the lithic carvings changed over time. The earliest and most primitive culture, Oldowan or Mode 1, appears in East African sediments around 2.4 Ma in the Early Paleolithic. Around 1.6 Ma appears a more advanced tradition, the Acheulean or Mode 2. The Mousterian culture or Mode 3 is the tool tradition that evolved from Acheulean culture during the Middle Paleolithic. Finally—for the limited purposes of this chapter—the Aurignacian culture, or Mode 4, appeared in the Upper Paleolithic. The original proposal of cultural modes by Grahame Clark (1969) included a Mode 5 by differentiating some technical details, allocating to Mode 4 the punch-struck blades from prismatic cores of the Upper Paleolithic, while the Mode 5 was reserved for the microliths and compound tools of the late Upper Paleolithic. We believe that this distinction is not necessary for the present chapter, whose aim is to relate cultural development to human evolution. A first approach attributes each cultural stage to a particular human taxon. Thus, the beginning of tool making, ie, Mode 1, is linked to *Homo habilis*, and "technology"—understood as the making of tools which require a modern mind necessary for Mode 4—to *Homo sapiens*. Although we will also examine the technical advances assigned to Mode 5 by Clark (1969), these are part of an evolution that does not involve a change of species. In fact, the "technology" may be adding new modes due to the multiple technological advances that the cultural evolution of *H. sapiens* has achieved, starting with agriculture. It doesn't make sense to suggest such a model, nor will we go into the later cultural developments that follow the evolution of the modern mind.

We should already express a methodological caveat before proceeding: the scheme Cultural Mode = species, is too general and incorrect. The assumption that a certain kind of hominin is the author of a specific set of tools is grounded on two complementary arguments: (1) the hominin specimens and lithic instruments were found at the same level of the same site; and (2) morphological interpretations attribute to those particular hominins the ability to manufacture the stone tools. The first kind of evidence is, obviously, circumstantial. Sites yield not only hominin remains, but those of a diverse fauna. The belief that our ancestors rather than other primates are responsible for the stone tools comes from the second type of argument, the capacity to manufacture. This consideration is perfectly characterized by the episode involving the discovery and proposal of the species *H. habilis*. As Louis et al. (1964) said, "When the skull of *Australopithecus (Zinjanthropus) boisei* was found [in Olduvai, Bed 1] no remains of any other type of hominid were known from the early part of the Olduvai sequence. It seemed reasonable, therefore, to assume that this skull represented the makers of the Oldowan culture. The subsequent discovery of *H. habilis* in association with the Oldowan culture at three other sites has considerably altered the position. While it is possible that *Zinjanthropus* and *H. habilis* both made stone tools, it is probable that the latter was the more advanced tool maker and that the *Zinjanthropus* skull represents an intruder (or a victim) on an *H. habilis* living site." (Leakey et al., 1964).

Here we have a clear example of the argumentative sequence: First, a *Paranthropus boisei* cranium and

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00044-2

associated lithic instruments were discovered at the FLK I site, Olduvai. Later, hominins with a notably greater cranial capacity, included in the new species *H. habilis*, were discovered at the same place. Eventually, stone tools were attributed to *H. habilis*, morphologically more advanced in its planning capacities. Leakey et al. (1964) paper included a cautionary note. Even though it is less probable, it is conceivable that *Zinjanthropus* also made lithic tools.

However, the attribution of capacities that identify *H. habilis* as the author of Olduvai lithic carvings has some reservations. John Napier (1962) published an article on the evolution of the hand two years before, relating stone tools to the discovery of 15 hominin hand bones by Louis and Mary Leakey at the site where *Zinjanthropus* had been found. According to Napier, "Prior to the discovery of *Zinjanthropus*, the South African man-apes (Australopithecines) had been associated at least indirectly with fabricated tools. Observers were reluctant to credit man-apes with being toolmakers, however, on the ground that they lacked an adequate cranial capacity. Now that hands as well as skulls have been found at the same site with undoubted tools, one can begin to correlate the evolution of the hand with the stage of culture and the size of the brain" (Napier, 1962).

Napier's (1962), and Leakey et al. (1964) interpretations of the Olduvai findings exemplifies the risks involved in the correlation of specimens and tools. Both the skull of *Zinjanthropus* (OH 5) as well as the OH 8 collection of hand and feet bones (with a clavicle), all of them found by the Leakey team in the same stratigraphic horizon, could be related to lithic making. Sites yielding tools and fossil samples of australopiths and *H. habilis* require deciding which of those taxa made the tools. The widespread attribution of Mode 1 to *H. habilis* is based on a set of indicators among which are hand morphology and size, as well as brain lateralization—an expression of the control capabilities of either hand—(Ambrose, 2001; Panger et al., 2002).

PRECULTURAL USES OF TOOLS

Regarding the use of stones or other materials for obtaining food, one must distinguish between two different operations. One matter is to make use of pebbles, sticks, bones, or any available object to, for example, break nutshells and access the fruit; another is to manufacture very deliberately tools with a specific shape to carry out a precise function. Although we are speaking in speculative terms, it is conceivable that the spontaneous use of objects as tools preceded stone carving.

By means of the comparative study of the behavior of African apes, ethology has provided some interesting interpretations about how chimpanzees use, and sometimes modify, stones and sticks to get food. Since the first evidence of such behaviors collected by Jane Goodall and Jordi Sabater Pi (Goodall, 1964; Sabater Pi, 1984), many cases of chimpanzee tool use that can be considered cultural have been brought to light. Very diverse cultural traditions have been documented, including up to 39 different behavioral patterns related with tool use by chimpanzees (Boesch and Tomasello, 1998; Vogel, 1999; Whiten et al., 1999). Some of these patterns include the use of different tools in sequence, as it is done by the Loango chimpanzees (Gabon) for obtaining honey (Boesc et al., 2009). It is, of course, true that the use of tools includes different patterns in the case of humans, who carry out operational planning tasks and, in particular, technical improvement processes (Davidson and McGrew, 2005). However, it is also true that chimpanzees are able to consider future uses of tools, which involves some planning (Mulcahy and Call, 2006). It has even been observed experimentally in these apes a conformity to cultural norms used by dominant individuals in the group, an attitude similar to human behaviors (Whiten et al., 2005).

One of the most interesting aspects of chimpanzee behavior, to understand the evolution of the lithic traditions, is the production, at the beginning unintentional, of flakes which resemble those produced by the first human cultures. This "spontaneous" production appears when chimpanzees accidentally shatter a stone while trying to crack nuts; the result can lead to sets of cores and flakes that are reminiscent of those in the oldest hominin sites containing tools (Mercader et al., 2002, 2007). It is reasonable to think that the hominins themselves would use, at least as much as chimpanzees, the spontaneous tools available (Panger et al., 2002). And they would do it for a considerable time before starting to produce tools explicitly. This idea was expressed by John Robinson (1962) when he said that the australopiths did not produce the complex carved stone found in Sterkfontein; but, for this author, this does not mean they lacked culture. When seeking food they could have used rocks, sticks, bones, and any other tools that would be useful for their purposes. Eudald Carbonell et al. (2007) have referred to these usages prior to tool production as the "biofunctional stage" or "Mode 0." Shannon McPherron et al. (2010) have identified at the site of Dikika (Ethiopia) stone tool–inflicted marks on bones whose age is more than 3.39 Ma. Even though McPherron et al. (2010) found no tools in Dikika, Sonia Harmand presented at the meeting of the Paleoanthropology Society in San Francisco on April 14, 2015, the finding at the site of Lomekwi (Lake Turkana, Kenya) of tools coming from sediments with an age of around 3.3 Ma (Callaway, 2015). There are, moreover, very heavy artifacts, some of them up to 33 lbs. Although at the time of writing this chapter the research on these tools has not been published, clues about the ancient use of stone tools are increasing.

It should be noted that suspicions about the existence of a distinct cultural level for australopiths were for a long time tied to evidence coming from Taung and Sterkfontein. The fractured bases of baboon skulls of Taung and other places, for example, indicated to Raymond Dart that they were cracked to consume their insides. Dart (1957) argued that the bones themselves had been used by australopiths as tools to strike, crush, and cut, giving rise to a tradition of using tools of "natural" origin, the osteodontokeratic culture prior to the use of stone tools.

Although the osteodontokeratic culture was eventually considered as a misinterpretation, and taphonomic studies would tend to argue that the identified bones were not actually tools, studies such as that of Francesco d'Errico and Lucinda Backwell (2003) on the uses of bones from Sterkfontein—members 1–3, between 1.8 and 1.0 Ma—have shown indications, in the form of wear marks, of their being used in milling tasks. In a later work, d'Errico and Backwell (2009) studied the different uses of bones. Once again, for the functions assigned to bones as tools, the use of sticks by chimpanzees in tasks such as digging, to extract termites or to separate the bark of trees, can serve as a model. Optical interferometer analysis of terminal areas of bones used as tools has revealed different wear patterns on specimens from Swartkrans and Drimolen. d'Errico and Backwell (2009) concluded that the differences found indicate diverse activities, as well as contacts with abrasive particles of various sizes, that would point to tasks similar to those that have been observed in chimpanzees.

The use of bones as tools extends to the African Middle Paleolithic, and even to the Upper Paleolithic, although with very different purposes to those inferred for tools of Swartkrans lower levels, as is evidenced, for example, by the small ivory points from Upper Semliki Valley, Zaire (Brooks et al., 1995; Yellen et al., 1995). The markings found on the bones have been used as evidence of butchering activities. If appropriate taphonomic considerations are taken into account, the markings observed on carcasses are an irrefutable proof of the use of cutting tools on them. However, according to Sherwood Washburn (1957) the accumulation of remains in the breccias of South African caves is unrelated to hominin butchering tasks. There is a predominance of mandibular and cranial remains because they are the bones most difficult to break, so that they tend to accumulate in the lairs of predators and scavengers. Ancestral hyenas are likely responsible for the accumulation of remains that we now find fossilized, australopiths included. It has been suggested that the Taung child itself was the victim of a predator, probably an eagle (Berger and Clarke, 1996), though this hypothesis has been criticized (Hedenström, 1995).

Manipulated stones cannot be attributed to predators. Many lithic instruments have been found at the Sterkfontein *Extension Site*—hand axes, cores, flakes, and even a spheroid—which are unequivocal signs of the manipulation of raw materials to obtain tools designed to cut and crush (Robinson and Manson, 1957). However, there are doubts regarding the association between stone tools and their authors. The sites that have provided *Australopithecus africanus*, Sterkfontein, Makapansgat and Taung, are not the only ones that have provided samples of an early lithic culture. There is also a stone industry at Swartkrans (Brain, 1970; Clarke et al., 1970), though it was found a long time after Dart elaborated his idea of hominization. The interpretation of the possible stone artifacts found at Kromdraai is not easy (Brain, 1958). But even in Sterkfontein, the *Extension Site* belongs to Member 5, whereas Member 4, older than 5, has provided a great number of *Au. africanus* specimens although it has yielded no lithic tool whatsoever.

If the accumulation of bones at Sterkfontein Member 4 was due to scavengers, and if australopiths were the hunted and not the hunters, the question concerning the first toolmakers remains unanswered. The answer will depend on preconceptions regarding cognitive capacities and hominin adaptive strategies. New kinds of evidence have bearing on this issue: the paleoclimate to which different genera and species were adapted; the morphology of certain key elements required for the intentional manipulation of objects, such as hands and the brain; the diet and the taphonomic study of the relation at the sites of bones and tools.

TAPHONOMIC INDICATIONS OF CULTURE

Paleoclimatological conclusions regarding early hominin taxa suggest they were adapted to tropical forests. This is the case of *Australopithecus anamensis* (Leakey et al., 1995), *Ardipithecus ramidus* (WoldeGabriel et al., 1994), *Australopithecus afarensis* (Kingston et al., 1994) and *Au. africanus* (Rayner et al., 1993). This argues against Raymond Dart's original hypothesis that related bipedalism, the expansion of open savannas, and the appearance of the first hominins. The first hominins would have emerged long before the expansion of the savanna in Africa and before any evidence of lithic tool use.

But in Dart's time no Miocene hominins were known, so it was logical that he spoke of "the first humans," referring to those who colonized the savanna during the Pliocene-Pleistocene. Which of them first began to use stone tools? Again, we are facing the necessity to associate fossil remains to the lithic tools found at the sites.

We said before that the attribution of a particular hominin taxon to the making of a specific culture type is based on finding the hominin specimens and lithic instruments at the same level of the same site. However, we must avoid falling into circularity. Especially, every precaution should be taken when attributing manipulation of ancient tools to hominins of different sympatric species. If

we find two taxa, T1 and T2, present at the same site and stratigraphic horizon—as happens with *H. habilis* and *P. boisei* at Olduvai—and if we claim that the authors of the carvings belong to one of them, let's say to T1, because we assume that they have the ability to make tools, we will be falling into a circular argumentation. When finding the tools, we assume that those who carved them are precisely those individuals to whom we had previously attributed the possession of a cognitive level and manual capacity for manufacturing them.

Circularity can be broken if in sites where the alleged authors, such as T1, are found, of the carvings, tools are also found in a fairly widespread way, while that is not the case for T2 or any other taxon, which only sporadically are found associated with tools. In that case, it is reasonable to accept T1 as the toolmaker.

The systematic coincidence between a specimen of a particular morphology and lithic carvings of a specific cultural tradition is what has led us to consider the first species of the genus *Homo* as responsible for the oldest culture.

With regard to South Africa, the issue is uncertain. Sterkfontein Member 5 has yielded the Stw 53 cranium, which, as we saw, is considered as either *H.* aff. *habilis* or an *Australopithecus* of an unspecified species; and it was considered as the specimen-type of *Homo gautengensis* by Darren Curnoe (2010). Swartkrans has also provided some exemplars attributed to *H. habilis* and, regarding Taung, the most widespread opinion argues that the stone tools are much more recent and that they were made by more evolved hominins.

The words "more evolved" obscure the circularity trap about which we spoke earlier. It makes us think that, as the carving of lithic tools imply high cognitive abilities, the presence of tools of that type leads us to conclude that their creators had reached a higher cognitive development. To accept that as a truth it is necessary to relate that "cognitive leap" with some other evidence aside from stone tools.

Taphonomic studies, which reconstruct the process of accumulation of available fossil evidence at a site, have enabled further progress in understanding the behavior of ancient hominins. Different sites in East Africa (Olduvai, Koobi Fora, Olorgesailie, Peninj) provide evidence of hominin habitation with direct association of hominin fossil remains and manipulated stones. As a result of such studies, Raymond Dart's idea of hominins as hunters in the open savanna was followed by the hypothesis that the first stone tool makers were scavengers who cooperated to a greater or lesser degree to obtain food (Binford, 1981; Blumenschine, 1987; Bunn, 1981; Isaac, 1978). The role of cooperation and the type of activity aimed to obtain meat are still controversial, and some authors advocate the idea that hominins associated to sites with ancient cultural presence were hunters rather than scavengers (for example, Domínguez-Rodrigo et al., 2007). In fact, the controversy is not decisive. Once again, it is reasonable to think that the first *Homo* were opportunists, and in their carnivorous behavior benefited from the available opportunities to both scavenge and hunt.

MODE 1: OLDOWAN CULTURE

Taphonomic studies, aimed at reconstructing the process of accumulation of available fossil evidence at a site, have increased our understanding of the behavior of early hominins. Different East African sites (Olduvai, Koobi Fora, Olorgesailie, Peninj) provide samples of hominin living sites with a direct association of hominin fossil remains and manipulated stones.

Although Olduvai gorge was not the first place in which early stone tools were found, it gave name to the earliest known lithic industry: Mode 1, also known as Oldowan culture. The excellent conditions of the Olduvai sites provided paleontologists and archaeologists with the chance to carry out taphonomic interpretations for reconstructing hominin habitats. Any lithic culture can be described as a set of diverse stones manipulated by hominins to obtain tools to cut, scrape, or hit. They are diverse tools obtained by hitting pebbles of different hard materials. Silex, quartz, flint, granite, and basalt are some of the materials used for tool making. In the Oldowan culture, the size of the round shaped cores is variable, but they usually fit comfortably in the hand; they are tennis ball–sized stones. Many tools belonging to different traditions fit within these generic characteristics. What specifically identifies Oldowan culture is that its tools are obtained with very few knocks, sometimes only one. The resultant tools are misleadingly crude. It is not easy to hit the stones with enough precision to obtain cutting edges and efficient flakes.

The Oldowan tools are usually classified by their shapes, with the understanding that differences in appearance imply different uses. Large tools include: (1) cobbles without cutting edge, but with obvious signs of being used to strike other stones, with the very appropriate name of hammerstones; (2) cobbles in which a cutting edge was obtained by striking, which served to break hard surfaces such as long bones (to reach the marrow, for example). They are called choppers; (3) flakes resulting from the blow to a core. Their edges are very sharp, as much as one of a metal tool, and their function is to cut skin, flesh, and the tendons of animals that need to be butchered. They can be retouched or not; (4) scrapers, retouched flakes with an edge which recall in some ways a serrated knife, and whose function would have been to scrape the skin into rawhide; (5) polyhedrons, spheroids, and discoids. Cores manipulated in various ways, as if flakes had been removed from their outer perimeter. Their function is uncertain; they may be nothing more than waste without particular utility.

It is not easy to arrive at definitive conclusions regarding the use of Oldowan tools. The idea we have of their function depends on the way we interpret the adaptation of hominins that used them, based on arguments that are often circular. Toolmakers can be seen, as Lewis Binford (1981) did, as a last stage in scavenging, when only large bones are available. If this were the case, the most important tools would be the hand axes that allow hitting a cranium or femur hard enough to break them. If, on the contrary, we understand that early hominins butchered almost whole animals, then flakes would be the essential tools. A functional explanation can be established between hand axes, manipulated with power grips, and flakes, which require handling them with the fingertips using a precision grip. It is not easy to go beyond this, but some authors, like Nicholas Toth (1985a,b), have carried out much more precise functional studies. Toth argued that flakes were enormously important for butchery tasks, even when they were unmodified, while he doubted the functional value of some polyhedrons and spheroids.

Several kinds of evidence have been used to resolve the question of how early hominins obtained animal proteins. One is the detailed analysis of the tools and their possible functionality. The microscopical examination of the edge of a lithic instrument allows inferring what it was used for—whether it served as a scraper to tan skin, or as a knife to cut meat, or as a hand axe to cut wood. This affords an explanation of behavior that goes beyond the possibilities of deducing a tool's function from its shape. In certain instances lithic tools might have been used as woodworking tools. Indications of the use of wood instruments are not rare in the Late Pleistocene. In the Middle Pleistocene, the finding of plant microremains (phytoliths, fibers) on the edges of Peninj (Tanzania) Acheulean bifaces is the earliest proof of processing of wood with artifacts (Dominguez-Rodrigo et al., 2001).

The examination of the marks that tools leave on fossil bones provides direct evidence of their function. Taphonomic interpretations of cutmarks suggest hominins defleshed and broke the bones to obtain food. This butchery function related to meat intake portrays early hominins as scavengers capable of taking advantage of the carcasses of the prey of savanna predators (Blumenschine, 1987). But in some instances the evidence suggests other hypotheses. Travis Pickering et al. (2000) analyzed the cutmarks inflicted by a stone tool on a right maxilla from locality Stw 53 at Sterkfontein Member 5. The species to which the specimen belongs is unclear, but it is certainly a hominin. They noted that "[t]he location of the marks on the lateral aspect of the zygomatic process of the maxilla is consistent with that expected from slicing through the masseter muscle, presumably to remove the mandible from the cranium." In other words, a hominin from Sterkfontein Member 5 dismembered the remains of another.

Are these marks indicative of cannibalistic practices, or are they signs of something like a ritual? The available evidence does not provide an answer to this question. It is not even possible to determine whether the hominin that disarticulated the Stw 53 mandible and its owner belonged to the same species. But cannibalistic behaviors have been inferred from Middle Pleistocene cutmarks. This is how the cutmarks on the Atapuerca (Spain) ATD6-96 mandible have been interpreted (Carbonell et al., 2005). It has also been suggested regarding the Zhoukoudian sample (Rolland, 2004). Cannibalism seems to have been common among Neandertals and the first anatomically modern humans.

The Oldowan culture is not restricted to Olduvai. Stone tools have also been found at older Kenyan and Ethiopian sites, though in some occasions their style was slightly different. These findings have extended back the estimated time for the appearance of lithic industries (Table 44.1). For a list of Mode 1 main sites, see Plummer (2004).

Close to 3000 artifacts were found in 1997 at the Lokalalei 2C site (West Turkana, Kenya), with an estimated age of 2.34 Ma. They were concentrated in a small area, about 10 square meters, and included a large number of small elements (measuring less than a centimeter) (Roche et al., 1999). The tools were found in association with some faunal remains, but these show no signs of having been manipulated. Nearby sites, LA2A, LA2B and LA2D, and the more distant LA1 have also provided stone tools; LA1 and LA2C, with an age of 2.34 Ma, are the oldest sites with utensils in Kenya (Tiercelin et al., 2010).

The importance of the Lokalalei tools lies primarily in the presence of abundant debris, which allows establishing the sequence of tool making in situ. Helene Roche et al. (1999) have argued that the technique used by the makers of these tools required very careful preparation and use of the materials, previously unimaginable for such early hominins. This suggested that the cognitive capacities of those toolmakers were more developed than what is usually believed. One of the cores was hit up to 20 times to extract flakes, and the careful choice of the materials (mostly volcanic lavas like basalt) indicates that those who manipulated them knew their mechanical properties well.

TABLE 44.1 The Oldest Cultures

Name	Localities	Age (Ma)
Lokalalei	West Turkana	2.34
Shungura	Omo	2.2–2.0
Hadar	Hadar	2.33
Gona	Middle Awash	2.5–2.6

Lokalalei findings indicate that hand control and, therefore, brain development, must have been already quite developed for nearly two and a half million years ago. The question of what species would have been responsible for manipulating these artifacts is a different matter, as we have repeatedly pointed out. James Steele (1999) raised the issue of the cognitive capacities and knowledge of the authors of the Lokalalei 2C tools. Steele admitted that the available evidence does not allow going beyond hypotheses similar to the one which attributed the Olduvai tools to *H. habilis* because of its larger cranial capacity compared with *P. boisei*. The Lokalalei findings indicate that almost two and a half million years ago the motor control of the hands, and thus the development of the brain, must have been considerable. The identity of the species responsible for manipulating those artifacts is a different issue, difficult to answer. In his commentary about Roche and colleagues' discovery, Steele (1999) refused to give a definitive answer. He simply argued that we still have similar doubts to those of the authors who, in 1964, associated the tools found at Olduvai with the species *H. habilis*.

The Middle Awash region includes many sites that have yielded Oldowan and Acheulean—a culture which replaced the Oldowan over time—tools, described for the first time by Maurice Taieb (1974) in his doctoral thesis. A *Homo* maxilla (AL 666-1) was found in association with Oldowan tools at Hadar (Ethiopia), to the north of Middle Awash. The sediments from the upper part of the Kada Hadar Member were estimated to 2.33 Ma; this was the earliest association between lithic industry and hominin remains (Kimbel et al., 1996). The 34 instruments found in the 1974 campaign (indicative of a low density of lithic remains) are typical of Oldowan culture: choppers and flakes. In addition, three primitive bifaces, known as end-choppers, appeared on the surface, but it is difficult to associate these tools with the excavated ones.

The earliest known instruments have been found at the Gona site (Ethiopia), within the Middle Awash area, in sediments dated to 2.6−2.5 Ma by correlation of the archaeological localities with sediments dated with the $^{40}Ar/^{39}Ar$ method and paleomagnetism (Semaw et al., 1997). Thus, they are about 200,000 years older than the Lokalalei tools.

Gona has provided numerous tools, up to 2970, including cores, flakes, and debris. Many of the tools were constructed in situ. No modified flakes have been found, but the industry appears very similar to the early samples from Olduvai. Sileshi Semaw et al. (1997) attributed the differences, such as the greater size of the Gona cores, to the distance between the site and the places where the raw materials (trachyte) were obtained; these are closer in Gona than in other instances. As hominins have not been found at the site, it is difficult to attribute the tools to any particular taxon. Semaw et al. (1997) believed it was unnecessary to suggest a "pre-Oldowan" industry. Rather, the Oldowan industry would have remained in stasis (presence without notable changes) for at least a million years. The precision of the Gona instruments led Sileshi Semaw's team to assume that their authors were not novices, so even earlier lithic industries might be discovered in the future.

That future may have already arrived. *Nature* (Callaway, 2015) has reported the finding of stone cores and flakes, likely intentionally crafted, at the Lomekwi site, west of Kenya's Lake Turkana. The sediments are dated 3.3 Ma, much older than *H. habilis*. Sonia Harmand of Stony Brook University in New York reported the findings at a meeting of the Paleoanthropology Society in San Francisco on April 14, 2015. Harmand's team concluded that the tools represent a distinct culture, which they have named the Lomekwian culture. Harmand pointed out at the meeting of the Paleoanthropology Society that the cores are enormous, some weighing as much as 15 kg, which is surprising considering the small size of the australopithecines. How could they handle such large stones? And what were they used for?

Bernard Wood (1997) wondered about the authors of the tools found at the site. The great stasis of the Oldowan culture suggested by the tools raises a problem for the usual assignation of the Oldowan tradition to *H. habilis*. Given that the latest Oldowan tools are about 1.5 -Ma old, this tradition spans close to a million years. This is why Wood (1997) noted that if Oldowan tools had to be attributed to a particular hominin, then the only species that was present during the whole interval was *P. boisei*. This is circumstantial evidence in favor of the notion that robust australopiths manufactured tools. But as we have mentioned several times in this book, there is no need for making a close identification between hominin species and lithic traditions, because cultural sharing must have been quite common. In any case, de Heinzelin et al. (1999) attributed the Gona utensils to the species *Australopithecus garhi*, whose specimens were found at Bouri, 96 -km south of where the tools come from.

The comparison between instruments from different sites has its limitations. As Glynn Isaac (1969) noted, it is not uncommon to find that the differences between the Oldowan techniques found at different locations of the same age are as large as those used to differentiate successive Oldowan stages, or even larger. This problem illustrates that the complexity of a lithic instrument is a function of its age, but also of the needs of the toolmaker.

THE TRANSITION MODE 1 (OLDOWAN) TO MODE 2 (ACHEULEAN)

Mode 2, or Acheulean culture, corresponds to a new carving procedure whose most characteristic element is the biface, "teardrop shaped in outline, biconvex in cross-section, and commonly manufactured on large (more than

10 cm) unifacially or bifacially flaked cobbles, flakes, and slabs" (Noll and Petraglia, 2003). These tools, made with great care, were identified for the first time at the St. Acheul site (France), and are known as "Acheulean industrial complex" or "Acheulean culture" (Mode 2). Acheulean culture appeared in East Africa over 1.7 Ma, and extended to the rest of the Old World reaching Europe, where the oldest Acheulean tools received the local name of "Abbevillian industry." The life of the Acheulean continued in Europe until about 50,000 years ago, although since 0.3 Ma more advanced utensils could be found from other cultural traditions, the Mousterian or Mode 3, which we will discuss later.

Mary Leakey (1975) described the transition observable at Olduvai from perfected Oldowan tools to a different and more advanced industry. The oldest instruments of Olduvai, which come from Bed I, were in a level dated by $^{40}K/^{40}Ar$ method at 1.7−1.76 Ma (Evernden and Curtiss, 1965). The first Acheulean tools are from Bed II. Between both beds there are tuffs, but the section that corresponds precisely to the time of the transition between the two cultures cannot be precisely dated (Isaac, 1969). If, in addition, we point out that both cultures overlap in Olduvai for a considerable time, with the concurrent presence of utensils from both Mode 1 and 2, the difficulties to determine the precise moment of the cultural transition increase. Nevertheless, a gradual transition from Oldowan culture to Acheulean culture was justified by the sequence established by Mary Leakey for the Olduvai beds (Table 44.2).

Louis Leakey (1951) had previously considered the coexistence of cultures and the evolution of Oldowan instruments as evidence of gradual change. However, subsequent studies painted another scenario. Glynn Isaac (1969) argued that the improvement of the necessary techniques to go from the Oldowan to the Acheulean traditions could not have taken place gradually. A completely new type of manipulation would have appeared with Acheulean culture, a true change in the way of carrying out the operations involved in tool making. A similar argument has been made by Sileshi Semaw et al. (2009) when interpreting the sequence of cultural change. Depending on the archaeological record of Gona (Ethiopia) and other African locations, Semaw et al. (2009) concluded that the Mode II would have arisen rather abruptly by a rapid transition from the Oldowan technique.

If so, it would be important to determine exactly when that jump forward occurred and to establish the temporal distribution of the different cultural traditions. Such detailed knowledge is not easy to achieve. The Olduvai site does not reveal precisely when the cultural change took place. The earliest instruments, from Bed I, are found in a level dated to 1.7−1.76 by the potassium/argon method (Evernden and Curtiss, 1965). The later Acheulean utensils appeared at the Kalambo Falls locality at Olduvai, in association with wood and coal materials. The age of these materials was estimated by the 14C method at 60,000 years (Vogel and Waterbolk, 1967). There are other volcanic tuffs between both points, but the 1.6 Ma interval between the most recent level and Kalambo Falls limits the precision of the chronometry. This period corresponds precisely to the time of the transition between both cultures (Isaac, 1969). If we take into account the evolution within Mode 1, with developed Oldowan tools that overlap in time with Acheulean ones, the difficulties involved in the description of the cultural change increase.

The technical evolution from Mode 1 to Mode 2 can also be studied at other places, such as the Humbu Formation from the Peninj site, to the west of Lake Natron (Tanzania). After the discovery made by the Leakys and Isaac in 1967, authors such as Amini Mturi (1987) or Kathy Schick and Nicholas Toth (1993) carried out research at the Natron area. Several Natron sites show a transition from Oldowan to Acheulean cultures close to 1.5 Ma (Schick and Toth, 1993). The correlation of the Peninj and Olduvai sediments allows the identification of the Oldowan/Acheulean transition with the upper strata of Bed II from Olduvai. But neither Olduvai nor the western area of Lake Natron allow a more precise estimate of the time of the change.

Another site excavated after the works at Olduvai and Peninj, Olorgesailie (Kenya), provided precise dating (by means of the $^{40}K/^{40}Ar$ method) for the Acheulean tools from Members 5 through 8 of that Formation, but they are recent sediments, estimated to between 0.70 and 0.75 Ma (Bye et al., 1987). The precise time of the substitution of Oldowan by Acheulean tools cannot be specified. Any group of hominins capable of using Acheulean techniques could have very well employed, on occasions,

TABLE 44.2 Cultural Sequence at Olduvai Established by Mary Leakey (1975, Modified)

Beds	Age in Ma	Number of Pieces	Industries
Masek	0.2	187	Acheulean
IV	0.7−0.2	686	Acheulean
		979	Developed Oldowan C
Middle part of III	1.5−0.7	99	Acheulean
		–	Developed Oldowan C
Middle part of II	1.7−1.5	683	Developed Oldowan A
I and lower part of II	1.9−1.7	537	Oldowan

simple tools to carry out tasks which did not require complex instruments.

An illustrative example is the large number of Acheulean artifacts found at Locality eight of the Gadeb site (Ethiopia) during the 1975 and 1977 campaigns. One thousand eight hundred forty-nine elements, including 251 hand axes and knives, were found at the 8A area, a very small excavation; whereas 20,267 artifacts appeared at 8E (Clark and Kurashina, 1979). The age estimates for the different Gadeb localities with lithic remains are imprecise: they range from 0.7 to 1.5 Ma. These localities contain, in addition to Acheulean tools, developed Oldowan utensils, which led J. Desmond Clark and Hiro Kurashina (1979) to conclude that two groups of hominins would have alternated at Gadeb, each with its own cultural tradition. But it is curious that the examination of the bones from Gadeb showed that the butchery activities had been carried out mostly with the more primitive hand axes, those belonging to developed Oldowan. This fact raises an alternative interpretation, namely, that tools obtained by advanced techniques are not necessary for defleshing tasks.

Konso-Gardula (Ethiopia), south of the River Awash and east of River Omo, has allowed the most precise dating of the beginning of the Acheulean culture. In addition, it has provided the oldest-known tools belonging to that culture. Since its discovery in 1991, Konso-Gardula has provided a great number of tools, which include rudimentary bifaces, trihedral-shaped burins, cores, and flakes, together with two hominin specimens, a molar and an almost complete left mandible (Asfaw et al., 1992). The sediments were dated by the $^{40}Ar/^{39}Ar$ method to 1.34−1.38 Ma (Asfaw et al., 1992). Berhane Asfaw and colleagues (1992) associate the Konso-Gardula hominin specimens with the *Homo ergaster* specimens from Koobi Fora, especially with KNM-ER 992.

THE ACHEULEAN TECHNIQUE

To what extent can the Acheulean tradition be considered a continuation or a rupture regarding Oldowan? Was developed Oldowan a transition phase toward subsequent cultures? Mary Leakey (1966) believed that developed Oldowan was associated with the presence of primitive hand axes, protobifaces that anticipated Acheulean bifaces. However, protobifaces cannot be strictly considered as a transitional form between Oldowan and Acheulean techniques. Marcel Otte (2003) argued that natural constraints (eg, mechanical laws of the raw materials) forces the manufacture of similar forms, which thus may be considered successive stages of a single or very close elaboration sequence, although this may not always be the case.

The successive manipulation of a core, passing through several steps until the desired tool is obtained, is a task that Leroi-Gourhan (1964) named *chaîne opératoire* ("working sequence"). While a chopper and a protobiface respond to the same *chaîne opératoire*, the manufacture of Acheulean bifaces is the result of a completely different way of designing and producing stone tools. The main objective of Oldowan technique was to produce an edge, with little concern for its shape. However, Acheulean bifaces had a very precise outline, which evinces the presence of design from the very beginning. The existence of design has favored speculation about the intentions of the toolmakers.

In the tradition of Leroi-Gourhan, Nathan Schlanger (1994) suggested that the sequence of operations in the making of tools reflects an intention and a mental level of some complexity. One might, accordingly, distinguish between two types of "knowledge":

- Practical knowledge, necessary for any carving operation. It is what psychologists call "procedural knowledge," as it is needed to ride a bicycle without falling.
- Abstract knowledge, or posing problems and their solutions. This is closer to "declarative knowledge," such as designing a route for cycling around town from one place to another with the least risk.

An easy way to distinguish between both is to understand that declarative knowledge can be transmitted through a spoken or written description, while the procedural knowledge cannot. However, as we will discuss, it is doubtful that the Acheulean culture involves accurate mental models of the tools that will be obtained, which brings into question the very *chaîne opératoire* of the Acheulean. The manufacture of accessories for transporting objects such as stones would be the real innovation of Mode 2 in that hypothesis.

Despite such doubts, the most common view holds that while a chopper and a protobiface belong to the same *chaîne opératoire*, obtaining Acheulean bifaces is the result of an entirely different approach when designing and producing a stone tool. The most conspicuous novelty is the diversity of Acheulean instruments. Sometimes it is difficult to assign a function to a stone tool. We have already seen that Oldowan *chaîne opératoire* and flakes have been interpreted both as simple debris and as valuable tools. However, Acheulean tools include knives, hammers, axes, and scrapers, whose function seems clear. The materials used to manufacture lithic instruments are also more varied within the new tradition. But the most notorious difference associated with the Acheulean culture is the tool we mentioned before: the hand axe.

The work of Glynn Isaac (1969, 1975, 1978, 1984) in Olorgesailie and Peninj (Tanzania) showed the main role of hand axes in the form of large flakes (Large Flake Acheulean, LFA) of more than 10 cm, in African Lower Paleolithic tool production. The study by Ignacio de la Torre et al. (2008) on the amount of raw material used for manufacturing various tools within two lithic sets found

in Peninj, RHS-Mugulud, and MHS-Bayasi, showed convincingly that the essential goal of hominins was to obtain large cutting tools, among which are the cleavers (without retouched edge), hand axes, and flakes, to use as knives. The carving technique used followed a characteristic pattern with a succession of steps not exclusive to Peninj carvings; it is the key to the Acheulean tradition:

1. The transformation of raw materials to be converted into cutting instruments involved, first, selecting suitable large stones to carve. The availability or lack of stone quarries with such raw materials may lead to significant differences between the cultural content of different sites.
2. Once the rock is selected, it is reduced by chipping off large flakes until obtaining still sizable blocks with a suitable form to begin careful carving.
3. The blocks are worked in *chaîne opératoire*, obtaining three different sizes of flake: small, medium, and large. The large flake, still of considerable size, is a hand axe in its basic shape which still needs a sharpened edge.
4. Larger flakes, which contrast with the intermediate ones by size, shape, and weight, are subjected to precision carving, with a number of successive blows to achieve its edge and final form: thus, an LFA appears. The number and accuracy of the blows contrast with the less systematic and manipulated of the protobifaces.

Peninj hand axes weighed, once finished, about 1 kg, so the waste materials from the large initial stones are abundant. In the intermediate stages of the Acheulean *chaîne opératoire*, flakes of different sizes are obtained, which can be in turn simultaneously used as tools for further carving. Smaller chips come from preparing the blocks or from shaping the hand axe. LFA production is complex and in most hand axes there are notches of 2–3 -cm long, which show that fragments, or chips, were knocked of—similar to those obtained intentionally in the Oldowan tradition—but they are actually the result of percussion while retouching. Medium-size flakes from LFA carving were found both in Olduvai and Peninj, although they are larger in the latter location (de la Torre et al., 2008). They are large but very thin flakes, so that their volume and weight are modest. They could have served for carving tasks or used as blades, just in the same condition as we have found them.

The most advanced Acheulean technique, with symmetrical bifaces and carefully carved edges, required a *soft-hammer* technique. This method consists in striking the stone core obtained in step 3 with a hammer of lesser hardness, such as of wood or bone. The blows delivered with such a tool allow a more precise control but requires, of course, much more labor. A detailed description of the process was provided by Schick and Toth (1993). The manipulation of large stones (mostly basalt and quartzite) for making hand axes seems to have been the turning point for the development of the Acheulean culture. Incidentally, it would also create a significant risk to those who had to manipulate stones of large size (Schick and Toth, 1993).

Schick and Toth (1993) noted that bifaces can also be obtained, in the absence of sufficiently large raw material, from smaller cores similar to those that served as a starting point for the manufacture of Oldowan choppers. But the manipulation of large blocks of material (mostly lava and quartzite) to produce long flakes seems to have been the turning point for the development of the Acheulean culture. It would also have involved risk for those who had to manipulate stones of large size (Schick and Toth, 1993).

The oldest Acheulean tool presence documented corresponds to the Kokiselei 4 site of Nachukui formation, West Turkana (Kenya). By radiometry of nearby volcanic tuffs ($^{40}Ar/^{39}Ar$), stratigraphic equivalence with Koobi Fora and paleomagnetism, Christopher Lepre et al. (2011) assigned to the terrain of Kokiselei 4 an age of 1.76 Ma. The site has the added advantage of also containing Oldowan utensils, which supports the idea that Mode 1 and Mode 2 technologies were not mutually exclusive. Lepre et al. (2011) argued as alternative hypotheses for the presence of Acheulean tools at Kokiselei 4, that they were either brought there from another location—unidentified yet—or carved by the same hominins of the site which produced Oldowan tools.

The last Acheulean utensils of East Africa, that is, the most recent, are from Kalambo Falls location (Tanzania), associated with coal and wood materials. The age of these materials was fixed by ^{14}C method at 60,000 years (Vogel and Waterbolk, 1967). With regard to South Africa, tools attributed to the Late Acheulan appear in various sites—Cape Hangklip, Canteen Kopje (stratum 2A), Montagu cave, Wonderwerk cave, Rooidam, Duinefontain 2, for example—with an age of ≈ 0.2 Ma (Kuman, 2007).

CULTURE AND DISPERSAL

The occasional presence of Oldowan tools is not proof indicating that a certain group had a primitive cultural condition. It is possible to find simple carvings in epochs and places that correspond to a more advanced industry. There is no reason to manufacture a biface by a long and complex process if what is needed at a given time is a simple flake. But the argument does not work in reverse. The presence of Mode 2 clearly indicates a technological development.

As we have seen, Oldowan culture is generally attributed to *H. habilis*. However, the identification of the Acheulean culture with the African *Homo erectus* is also very common. The strength of the bond of Acheulean/*erectus* led Louis Leakey to consider the emergence of Acheulean tools at Olduvai as the result of an invasion by

H. erectus from other localities (Isaac, 1969). Fossils of the taxon *H. habilis* are African, but numerous exemplars which can be attributed to *H. erectus* have appeared out of Africa. In fact, the taxon was named by Eugène Dubois (1894) from fossils found in Trinil, Java. Asians and African specimens had remarkable similarities, but also some differences, a fact that has led to the proposal of the species *H. ergaster* for the African *erectus* (Groves and Mazák, 1975). Although there is no general consensus on the need for that distinct taxon, those who deny the validity of *H. ergaster* commonly refer to Asian *erectus* as *H. erectus* sensus stricto, and to the African as *H. erectus* sensu lato.

Why is it necessary to propose two different species, or two degrees of the same species, when referring to *H. erectus*? One of the main reasons for the need to distinguish two groups of populations has to do with the culture. The oldest *H. erectus* of Java and China, unlike their coetaneous in Africa, did not exhibit Mode 2 culture.

Obviously, the occupation of Asia began with one or more African hominin dispersals. The natural way out of Africa is the Levantine corridor—Middle and Near East—a path that is widely understood as the one used by hominins during their various departures from the African continent. Located between the Black Sea and the Caspian Sea, Georgia is part of the transit area between Africa, Asia, and Europe. A site in Georgia, Dmanisi, has provided the best existing evidence to characterize the first hominin exit from their continent of origin. Since the initial discovery of a jaw, D211 (Gabunia and Vekua, 1995) in Dmanisi, other cranial specimens have appeared, such as D2280 and D2282 (Gabunia et al., 2000), of modest volume—775 and 650 cm^3 respectively. In 2002 the existence of another cranium of the same age, D2700, was reported (Vekua et al., 2002) that had an even smaller volume: 600 cm^3. We offer these details to contextualize the problem of attributing to which species these fossils belong. After hesitating to attribute them to *H. habilis* or *H. ergaster*, Léo Gabunia et al. (2002) proposed for Dmanisi hominins a new species: *Homo georgicus*. Two more exemplars, a cranium D3444 and its associated jaw D3900, were discovered in 2002–2004 campaigns (Lordkipanidze et al., 2005, 2006). New postcranial specimens from Dmanisi, belonging to an adolescent and three adults, one of large size and two smaller, were described in 2007 (Lordkipanidze et al., 2007). Although the authors did not ascribe the remains to any particular species, they indicated that the Dmanisi set lack those derived features characteristic of *H. erectus*.

Besides these fossils, from Dmanisi also come stone artifacts and animal bones with cutting and percussion marks. More than 8000—some choppers and scrapers, and abundant flakes—have been found in the two stratigraphic units, A and B, of the site. Reid Ferring et al. (2011) maintained that the stratigraphic study of the Dmanisi set of lithic utensils indicates that this place was repeatedly occupied during the last segment of the Olduvai subchron, ie, between the range of 1.85–1.78 Ma. In the authors' opinion, such an antiquity implies that the Georgia specimens precede the African *H. erectus* or *H. ergaster* emergence.

But Dmanisi is not the only site providing us with evidence of the migration out of the African continent. In the Yiron site, to the North of Israel near the valley of the Jordan River, instruments were found in 1981 consisting of flakes of a very primitive appearance, adding to other more modern tools previously found. The primitive artifacts were found in the stratigraphic horizon below the basaltic volcanic intrusion dated by radiometry at 2.4 Ma, thus the age of Yiron tools was considered comparable to the oldest culture of Mode 1 from the Rift (Ronen, 2006).

At least four other sites in Israel have provided old lithic utensils. Chronologically, Yiron is followed by the Erk-el-Ahmar formation, a few kilometers south of Ubeidiya, also in the Jordan Valley, where cores and silex flakes were found (Tchernov, 1999). After a few failures to date it by paleomagnetism, the magnetostratigraphy of the Erk-el-Ahmar formation made by Hagai Ron and Shaul Levi (2001) correlated the normal events of the area with the Olduvai subchron, attributing it thus an age of 1.96–1.78 Ma. However, the tools appeared at 1.5 km from the collected samples. Ron and Levi (Ron and Levi, 2001) accepted an age for the silex utensils of 1.7–2.0 Ma, a date supported by fauna studies (Tchernov, 1987), and that, by the way, is coincident with that of Dmanisi. Ubeidiya (Israel) is a locality between Yiron and Erk-el-Ahmar. Between 1959 and 1999, numerous lithic instruments were found, similar in age and appearance to those at the Oldowan–Acheulean transition of Olduvai Bed II, along with cranial fragments, a molar, and an incisor attributed *Homo* sp. indet (Tobias, 1966), or to *Homo* cf. *erectus* (Tchernov, 1986). An additional incisor was described in 2002 (Belmaker et al., 2002). The horizon with hominin remains was dated by fauna comparisons and stratigraphic study at ≈1.4 Ma, on the basis of the deposits age and tooth similarities with KNM-ER 15000 and the Dmanisi specimens. Miriam Belmaker et al. (2002) maintained that the last incisor found in Ubeidiya, UB 335, could be tentatively identified as *H. ergaster*. The utensils from Gesher Benot Ya'aqov are 0.8 Ma of age, dated by paleomagnetism. Finally, utensils found in Bizat Ruhama are younger than Gesher Benot Ya'aqov, which belongs to the lower part of the Matuyama chron (in both cases the information comes from Ronen, 2006).

All the tools found in these sites, which indicate the first dispersals out of Africa, are of Mode 1. Around 1.7–1.6 Ma hominins undertook various successful dispersals throughout Asia, reaching the Southeast—Java (Indonesia)—and the Far East—China. This means that vast zones of the Asian continent were occupied without

Acheulean utensils. However, later migrations brought Mode 2 out of Africa as well.

Acheulean instruments have a geographical eastern limit in the Indian subcontinent. With a detailed compilation of all the available evidence at that time, Hallam Movius (1948) established two areas: the first in Africa, West Asia, and West Europe, and the second ranging from the Far East to Southeast Asia. During the Middle Pleistocene, both had lithic industries, corresponding to different technical levels: choppers—ie, Mode 1—in the East, and bifaces—Mode 2—in the West. This is known as the "Movius line," the virtual limit that separates these two vast areas.

The Movius line was not a permanent obstacle for a long period of time. Truman Simanjuntak et al. (2010) claimed that around 0.8 Ma a noticeable change occurred in Java, when tools emerged which have been classified as Acheulean by these authors. Ngebung cleavers are the oldest indication, followed by the three human occupations of Song Terus cave (Punung, East Java), among which the "Terus period," of 0.3 to c. 0.1 Ma, is the oldest (Simanjuntak et al., 2010). Other Southeast Asian locations which also contain ancient lithic utensils are the island of Flores (Mata Menge site), with an age of 0.88−0.8 Ma obtained by fission track (Morwood et al., 1998), Bukit Bunuh (Malaysia), Ogan (Sumatra), Sembiran (Bali), Nulbaki (West Timor), Wallanae (Sulawesi) and Arubo (Luzon, Philippines) (Simanjuntak et al., 2010), as sufficient examples of a Mode 2 late dispersal. The overview of the various described industries of Southeast Asia led Sheila Mishra et al. (2010) to draw several somewhat controversial conclusions with regard to cultural dispersion. First, that Mode 2 reached Java and other Asian areas. Second, an indicative sequence of an initial period with an absence of large hand axes does not actually exist in India; all occupations of Southeast Asia would have had the set *H. erectus*/LFA as a protagonist. Third, a more bold assumption, India might have been both the origin of Mode 2 and of *H. erectus*, as well as the source of what later would become their African counterparts (*H. ergaster* and the Acheulean technique) by a reverse dispersal from Asia to Africa.

Regarding China, the oldest tools come from the basins of Yuanmou and Nihewan. Majuangou, the eastern border of the Nihewan basin has four stratigraphic horizons in which Mode 1 utensils have appeared, which are, from top to bottom, Banshan, MJG-I, MJG-II, and MJG-III (Table 44.3).

In accordance with paleomagnetic studies, the four beds with tools of Majuangou are distributed over 340,000 years, between Olduvai and Cobb Mountain subchrons. Fossils of mollusk shells and aquatic plants indicate a lacustrine environment. The lower bed is of 1.66 Ma (Zhu et al., 2004).

In the Yangtze riverbed, Sichuan province, is Longgupo site, with Mode 1 instruments of an uncertain age. They could be 1.9−1.7 Ma, in accordance to paleomagnetism (Wanpo et al., 1995), but electron spin resonance analysis on the cave specimens' dental enamel have indicated a much later date.

Cultural indications of very ancient human presence exist at Yuanmou, with four members, which are, from the oldest to the youngest, M1 (lacustrine and fluviolacustrine deposits), M2 (fluvial), M3 (fluvial), and M4 (fluvial and alluvial) (Zhu et al., 2008). The Member M4 in Niujiangbao has provided hominin remains and four stone tools which were found in 1973: a scraper, a small biface core, and two flakes of Mode 1 with evidence of laborious production (Yuan et al., 1984).

All the utensils of the described Chinese sites belong to Mode 1 (Oldowan). However, it has been claimed that tools from more modern locations correspond to Mode 2. Thus, Yamei et al. (2000) pointed out the presence at various sites in Bose basin, Guanxi province in Southern China, of more advanced tools. Although two-thirds of the basin contain only monoface tools, from the western area of Bose—in which the adequate raw material exists—come large cutting tools bifaces of 803,000 ± 3000 years of age, described by Yamei et al. (2000). According to that presence, Yamei et al. (2000) affirm that "Acheulean-like tools in the mid-Pleistocene of South China imply that Mode 2 technical advances were manifested in East Asia contemporaneously with handaxe technology in Africa and western Eurasia."

In the same Bose basin, but in its northern zone—Fengshudao site—were found an industry set with an abundance of hand axes, although smaller in size, of an age of 0.8 Ma, obtained by the $^{40}Ar/^{39}Ar$ method (Zhang et al., 2010). Pu Zhang et al. (2010) attributed these

TABLE 44.3 Stratigraphic Horizons With Lithic Tools of Majuangou (Zhu et al., 2004)

Bed	Location	Area (m^2) × Depth (in cm) of the Excavation	Year	Number of Tools
Banshan	44.3−45 m	2 × 70	1990	95
MJG-I	65.0−65.5	20 × 50	1993	111
MJG-II	73.2−73.56	40 × 36	2001−2002	226
MJG-III	75.0−75.5	85 × 50	2001−2002	443

characteristics to Fengshudao industry and, in particular, the absence of cleavers due to the lack of adequate raw material (big blocks). In their view, the tools correspond to the variability of the Acheulean, with its own particularities, such as unidirectional carving.

AN ANCIENT MODE 2 IN ASIA?

The cultural dispersal hypotheses, as the one by Sheila Mishra et al. (2010) mentioned before, or any other argument in favor of an ancient Mode 2 in the Far East (Java and China), such as that of Hou Yamei et al. (2000), stumble upon the idea of Asia colonization, which is widely accepted as the most probable and based on the Movius model. In fact, the controversy between the idea of an ancient presence of LFA in Java and the Movius line is more substantial. Mishra et al., in a paper of 2010 as well as in other previous works, denied the presence of different *chaînes opératoires* characteristics of Mode 1 and Mode 2, which is tantamount to denying the distinction between these two techniques. If it is the same industry with a higher or lesser development encompassing the entire ancient world, then the Movius line lacks meaning. However, in spite of the limitations of a simple geographic scheme, the common view accepts the Movius line, although its meaning has been much debated and there are still details to be explained, such as the absence of bifaces in Eastern Europe.

A cultural dispersal synthesis of the Middle Paleolithic highlights the following points indicated by Ofer Bar-Yosef and Miriam Belmaker (2011):

- absence of Acheulean culture in Southeast Asia
- presence in numerous locations of Mode 2 in Western Asia—Near East—decreasing abundance of bifaces as we approach the East—Caucasus and Anatolia
- discontinuity between the two areas with evident presence of Mode 2, the Levant, and India
- absence of Mode 2 in China, with the exception of Bose basin

The best explanation for cultural dispersal patterns of that kind requires that migrations from and to the west were discontinuous, in subsequent waves. But the evidence in relation to Java indicated by Sheila Mishra et al. (2010) cannot be thus justified. Critiques, like that of Parth Chauhan (2010), point to an incorrect age estimation due to inherent dating problems of the $^{230}Th/^{234}U$ technique. Although it is possible that the Acheulean arrived in Southeast Asia as early as the Brunhes-Matuyama limit, ie, 0.78 Ma, additional evidence is required.

Naturally, the problem of cultural dispersal doesn't end with the absence or presence of Mode 2 in the Far East. Indeed, local particularities lead to the need to make more precise distinctions to account for what was an evolution subject to large population movements. As Marcel Otte (2010) has said, the Movius line exists, rather, as a frontier, it is like a veil which moves as time passes by the hand of ethnic traditions. Neither these should be confused with carving techniques, nor is it possible to identify a biface or hand axe with an Acheulean utensil. In the strictest sense, Mode 2 refers to a specific *chaîne opératoire* which never is the first to appear in a site, nor is it required to be exclusive, because it can coexist with simpler carvings. Otte (2010) recognized that, exceptionally, bifaces are present in the Middle Paleolithic of China, but a close look at Bose hand axes led him to argue that they cannot be considered Mode 2 at all. They would be the result of a *discovery*: from cores of adequate origin, bifaces could be obtained with not much manipulation. The procedure is the opposite of Olorgesailie or Peninj technique, in which a huge block is flaked to obtain LFA. In an unfortunate expression, Marcel Otte (2010) qualified the Chinese Acheulean as a "research artifact." In the best of cases, it could be considered as cultural parallelism.

THE TRANSITION MODE 2 (ACHEULEAN) TO MODE 3 (MOUSTERIAN)

Mode 3, or Mousterian culture, is the lithic tool tradition that evolved in Europe from Acheulean culture during the Middle Paleolithic. The name comes from the Le Moustier site (Dordogne, France), and was given by the prehistorian Gabriel de Mortillet in the 19th century, when he divided the Stone Age known at the time in different periods according to the technologies he had identified (Mortillet, 1897). Mortillet introduced the terms Mousterian, Aurignacian, and Magdalenian, in order of increasing complexity, to designate the tools from the French sites of Le Moustier, Aurignac, and La Magdalene. However, as we said earlier, almost all the sites belonging to the Würm glacial period mentioned in the previous chapter contain Mousterian tools. In many instances, their lower archaeological levels also show the transition of Acheulean to Mousterian tools, and even from the latter to Aurignacian ones. The archaeological richness and sedimentary breadth of some of these sites, like La Ferrassie, La Quina, and Combe-Grenal, grants them a special interest for studying the interaction between cultural utensils and adaptive responses. Most European sites belonging to the Würm glacial period contain Mousterian tools. Similar utensils have appeared in the Near East, at Tabun, Skuhl, and Qafzeh.

Mousterian techniques changed in time. Geoffrey Clark's (1997) study of the Middle and Upper Paleolithic cultural stages convincingly demonstrated how wrong it is to speak about "Mousterian" as a closed tradition, with precise limits, or as a unit with precise temporal boundaries. Even so, we will talk about a Mousterian style, as Clark

himself did, which becomes apparent when compared with the Upper Paleolithic technical and artistic innovations which constitute Mode 4. However, to understand the magnitude of Mode 3, we must extend the consideration of "Mousterian culture" from lithic tools to other products and techniques that appear at Mousterian sites. In a broad sense, Mode 3 culture includes controversial features, such as objects created with a decorative intention and indications of funerary practices.

Let us begin with the Mousterian tool-making techniques. They were used to produce tools that were much more specialized than Acheulean ones, The most typical Mousterian tools found in Europe and the Near East are flakes produced by means of the Levallois technique, which were subsequently modified to produce diverse and shaper edges. Objects made from bone are less frequent, but up to 60 types of flakes and stone foils can be identified, which served different functions (Bordes, 1979).

The Levallois technique appeared during the Acheulean period, and was used ever since. The oldest Levallois carvings are probably c. 400 ka and come from the Lake Baringo region (Kenya) (Tryon, 2006). Its pinnacle was reached during the Mousterian culture. The purpose of this technique is to produce flakes or foils with a very precise shape from stone cores that serve as raw material. The cores must first be carefully prepared by trimming their edges to remove small flakes until the core has the correct shape. Thereafter, with the last blow, the desired flake—a Levallois point, for instance—is obtained. The final results of the process, which include points, scrapers, and other instruments, are subsequently modified to sharpen their edges. The amazing care with which the material was worked constitutes, according to Bordes (1953), evidence that these tools were intended to last for a long time in a permanent living location.

Tools obtained by means of the Levallois technique are, as we said earlier, typical of European and Near East Mousterian sites. Bifaces, on the contrary—so abundant in Acheulean sites—are scarce. The difference has to do mostly with the manipulation of the tools; scrapers were already produced using Acheulean, and even Oldowan, techniques. The novelty lies in the abundance and the careful tool retouching.

NEANDERTALS AND MOUSTERIAN CULTURE

Both in spatial and temporal terms, the Mousterian culture coincides with Neandertals. This identification between the Mousterian culture and *Homo neanderthalensis* has been considered so consistent that, repeatedly, European sites yielding no human specimens, or with scarce and fragmented remains, were attributed to Neandertals on the sole basis of the presence of Mousterian utensils. Despite the difficulties inherent in associating a given species with a cultural tradition, it was beyond doubt that Mousterian culture was part of the Neandertal identity. Exclusively?

This perception changed with the reinterpretation of the Near East sites (Bar-Yosef and Vandermeersch, 1993). Scrapers and Levallois points, which were very similar to the typical European ones, turned up there. Neandertals also existed there, of course, but in contrast with European sites a distinction could not be drawn between localities that had housed Neandertals and anatomically modern humans solely on the grounds of the cultural traditions. The more or less systematic distinction between Neandertal—Mousterian and Cro-Magnon—Aurignacian helped to clarify the situation in Europe. But it could not be transferred to the Near East, where sites occupied by Neandertals and those inhabited by anatomically modern humans, proto-Cro-Magnons, yielded the same Mousterian tradition utensils.

This coincidence implies several things. First, that cultural sharing was common during the Middle Paleolithic, at least in Levant sites. Second, that during the initial stages of their occupation of the eastern shore of the Mediterranean, anatomically modern humans made use of the same utensils as Neandertals. Hence, it seems that at the time Skuhl and Qafzeh were inhabited, there was no technical superiority of modern humans over Neandertals. The third and most important implication has to do with the inferences that can be made because Neandertals and *H. sapiens* shared identical tool-making techniques. As we have already seen, the interpretation of the mental processes involved in the production of tools suggests that complex mental capabilities are required to produce stone tools. We are now presented with solid proof that Neandertals and modern humans shared techniques. Does this mean that Neandertal cognitive abilities to produce tools were as complex as those currently characteristic of our own species? Many authors, headed by Trinkaus, Howells, and Zilhão, believe so. But some authors arguing in favor of high cognitive capacities in Neandertals went beyond lithic culture shared at the Near East. They presented other kinds of items which, in their opinion, were indications of Neandertal aesthetic, religious, symbolic, and even maybe linguistic, capacities.

The possibility that Neandertals buried their dead is the best basis to attribute transcendental thought to them. Voluntary burial is indicative of respect and appreciation, as well as a way to hide the body from scavengers. This may also imply concern about death, about what lies beyond death, and the meaning of existence. The argument for religiousness is convincing when burial is accompanied by some sort of ritual.

Neandertal burials have been located in four areas: Southern France, Northern Balkan, the Near East (Israel and Syria), and Central Asia (Iraq, Caucasus, and Uzbekistan). In most cases these burials seem to be deliberate.

Hence, the "old man" from La-Chapelle aux Saints appeared in a rectangular hole dug in the ground of a cave that could not be attributed to natural processes (Bouyssonie et al., 1908). In regard to La Ferrassie and Shanidar, the possible evidence of the existence of tombs led Michael Day (1986) to remark, in a technical and unspeculative treatise, that these exemplify the first intentional Neandertal burial that has been reliably determined. Eric Trinkaus' (1983) taphonomic considerations point in the same direction. The abundance and excellent state of Neandertal remains at those sites, together with the presence of infantile remains, are proof that the bodies were out of the reach of scavengers. Given that there is no way natural forces could produce those burials, Trinkaus believes the most reasonable option is to accept that the remains were intentionally deposited in tombs. However, William Noble and Ian Davidson (1996) argued that, at least in the case of Shanidar (Iraq), it is probable that the cave's ceiling collapsed while its inhabitants were sleeping.

Some of the aforementioned remains are not only buried intentionally, but they are accompanied by evidence of rituals. This is the case of the Kebara skeleton (Israel), which, despite being excellently preserved—it even includes the hyoid bone—is lacking the cranium. Everything suggests that the absence of the cranium is due to deliberate action carried out many months after the individual died (Bar-Yosef and Vandermeersch, 1993). It is difficult to imagine a different taphonomic explanation. Bar-Yosef and Vandermeersch (1993) wondered about the reasons for such an action, suggesting that the answer might lie in a religious ritual.

A Neandertal tomb with an infantile specimen was found in the Dederiyeh cave (Syria), 400 -km north of Damascus. Takeru Akazawa et al. (1995) interpreted the burial as an indication of the existence of a ritual. The reason behind this argument is the posture in which the specimen was deposited in the tomb. The excellently preserved skeleton was found with extended arms and flexed legs. Mousterian lithic industry also turned up in the cave, which Akazawa et al. (1995) associated with that from Kebara and Tabun B, though there were few tools at the burial level. An almost rectangular limestone rock was placed on the skeleton's cranium, and a small triangular piece of flint appeared where the heart had once been. Although Akazawa et al. (1995) did not elaborate an interpretation of these findings, they implicitly suggest that these objects had ritual significance.

The Shanidar IV specimen is one of the most frequent references in relation to ritual behaviors. The discovery of substantial amounts of pollen at the tomb was interpreted as evidence of an intentional floral offering (Leroi-Gourhan, 1975). If this were the case, it would represent the beginning of a custom that lasts today. It must not be forgotten either that two of the Shanidar crania, I and V, show a deformation that was attributed to aesthetic or cultural motives. However, Chris Stringer and Eric Trinkaus (1981) indicated that the specimens had been reconstructed incorrectly and that the shape of the first one was due to pathological circumstances. In his study of the Shanidar IV burial, Ralph Solecki (975) argued that there is no evidence of an intentional deposit of flowers at the burial. The pollen must have been deposited there in a natural way by the wind. Supporting the notion of an unintentional presence, Robert Gargett (1989) suggested that the pollen could have been introduced simply by the boots of the workers at the cave's excavation. Paul Mellars (1996) believes that the accidental presence of objects at French burial sites, such as La Ferrassie or Le Moustier, is inevitable: the tombs were opened at places in which faunal remains and Mousterian utensils were abundant.

The Teshik-Tash site (Uzbekistan), located on high and precipitous terrain, contains an infantile burial associated with wild goat crania. According to Hallam Movius (1953), the horns formed a circle around the tomb. This would support a symbolic purpose and a ritual content associated with the burial. Currently, however, even those who favor Neandertals as individuals with remarkable cognitive capacities are quite skeptical about the presumed intentional arrangement of the crania (Trinkaus and Shipman, 1993; Akazawa et al., 1995; Mellars, 1996).

Neandertal burials can be interpreted as a functional response to the need of disposing of the bodies, even if only for hygienic reasons. But they could also be understood as the reflection of transcendent thinking, beyond the simple human motivation of preserving the bodies of deceased loved ones. According to Mellars (1996), "we must assume that the act of deliberate burial implies the existence of some kind of strong social or emotional bonds within Neandertal societies." However, Mellars believes that there is no evidence of rituals or other symbolic elements in those tombs. The appearance of such evidence would demonstrate that Neandertals were capable of religious thinking. Similarly, Gargett (1989) argued that the evidence of Neandertal burials is much more solid than the evidence of offering or rituals. Julien Riel-Salvatore and Geoffrey A. Clark (2001) have noted that applying Gargett's criterion to the Early Upper Paleolithic would also lead to doubting the intentionality of the first modern human burials. They believe that there is a continuity, regarding the tombs, between the Middle and Early Upper Paleolithic archaeological records. True differences do not appear until the Late phase of the Upper Paleolithic (20−10 ka).

However, Neandertal burials contrast sharply with the burials made by modern humans, living approximately at the same time. The differences are especially illustrative in the Near East. The only intentional, and potentially symbolic, funerary Middle Paleolithic objects are the bovid and pig remains found in burials at Qafzeh and Skuhl

(Mellars, 1996). Both appeared in modern human sites. Taking into account that humans and Neandertals living at those sites shared the same Mousterian tradition, this is a significant difference. It not only has to do with the manufacture of objects, but with much more subtle aspects, which are associated with mental processes like symbolism, aesthetics, or religious beliefs.

William Noble and Ian Davidson (1996) stressed that Neandertal burials have not been found outside caves. In contrast, there are examples of very early human tombs in open terrains at places such as Lake Mungo (Australia), Dolni Vestonice (Czech Republic) and Sungir (Russia). In Noble and Davidson's (1996) view, the appearance of a Neandertal tomb outside the caves would be the best proof that this is an intentional burial. For now, known tombs provide no conclusive clues about Neandertal self-awareness, not to speak of their religion.

THE TRANSITION MODE 3 (MOUSTERIAN) TO MODE 4 (AURIGNACIAN)

The Mode 3, ie, the Mousterian culture characteristic of the Neandertals in Europe and Near East Asia during the Middle Paleolithic, ranged from about 100 to 40 ka. Around these dates more developed technocomplexes appeared in Europe. Industries called "transitional," to contrast them with the "real" Mode 4, a set of cultural traditions of the Upper Paleolithic, coincided with the entry of the first modern humans, the Cro-Magnon, into Europe between 40 and 28 ka. Traditions of the Upper Paleolithic include not only tools that are more precise and sophisticated than those from the earlier Mousterian culture but also abundant representations of real objects in the form of engravings, paintings, and sculptures, realistic representations that display significant differences in favor of the development of Mode 4. A good example is the large mammal paintings of the Chauvet cave, dated by radiocarbon calibration (^{14}C) at c. 36 ka (von Petzinger and Nowell, 2014). Such a realistic intensity of the polychromes of the Upper Paleolithic have led to the argument that modern humans achieved an artistic revolution explainable only by a corresponding cognitive revolution attaining what we call the "modern mind." Does this cognitive revolution appear suddenly and exclusively in our species?

As McBrearty and Brooks (2000) pointed out, the proposal of a cognitive revolution repeats a scenario introduced in the 19th century with the Age of the Reindeer (Lartet and Christy, 1865–1875). Around the 1920s the Upper Paleolithic was generally characterized by the presence of sculptures, paintings, and bone utensils. But according to McBrearty and Brooks (2000), the evidence used to determine the changes between the Lower, Middle, and Upper Paleolithic was always taken from the Western Europe archaeological record. During the last glacial period, the human occupation of that area was irregular, as F. Clark Howell (1952) pointed out, with populations periodically reduced, or even extinguished. McBrearty and Brooks (2000) argued that the "revolutionary" nature of the European Upper Paleolithic is mainly due to the discontinuity in the archaeological record, rather than to cultural, cognitive, and biological transformations, as suggested by advocates of the "human revolution." Instead, McBrearty and Brooks (2000) hold that there was a long process that gradually led to the European Aurignacian richness.

Was the transition to the European Aurignacian gradual or sudden? To analyze the process of change from Mode 4 to Mode 5, which is the same as specifying the time and mode of the emergence of the modern mind, we need to clarify a number of interrelated processes:

- the appearance of *H. sapiens*
- its dispersal from the place of origin
- cultural development leading to the industries of the European Upper Paleolithic

The first step to clarify the origin of the modern mind raises the issue of identification of the oldest members of our species. The name Cro-Magnon corresponds to fossils discovered in 1868 near Eyzies-de-Tayac (Dordogne), of c. 30 ka of age, obtained by comparison with ^{14}C date of the Aurignacian levels of the Pataud rock shelter (Dordogne) (Henry-Gambier, 2002), but applied in general to the first modern humans which entered Europe. The first entry could have been around ≈45 ka (Paul Mellars, 2005) (we will come back later to this issue). However, the age of *H. sapiens* would be considerably older. The numbers obtained by molecular methods have a remarkably broad range: 290–140 ka (Cann et al., 1987); 249–166 ka (Vigilant et al., 1991) obtained by coalescence of mtDNA. But, the paleontological record contains exemplars tentatively attributed to *H. sapiens* of much older age. The 640 ka old specimens from Bodo (Clark et al., 1994), if the "Bodo man" is thought to be a modern human, would make the origin of *H. sapiens* much older. The origin of our species would go even further back if the Danakil specimen, with almost a million years of age (Abbate et al., 1998), is included. All these fossils, besides their dubious ascription, are of a very different age than that indicated by molecular methods.

If we merely consider those specimens whose attribution to our species is most likely, various cranial materials from Aduma region (Middle Awash) should be mentioned, including the partial skull ADU-VP-1/3. Found on the surface, their age was attributed by morphological comparisons. When Yohannes Haile-Selassie et al. introduced them, they claimed that these crania "are similar in preserved parts to specimens from the Middle East, and from

northern and eastern Africa, between 100 and 300 ka. Specifically, the most complete Aduma cranium is most similar to crania thought to belong to the younger part of that range. This Middle Stone Age cranium, in most of its characters, is indistinguishable from other anatomically modern human crania" (Haile-Selassie et al., 2004). From the same formation, found on the surface, is the parietal BOU-VP-5/1, also attributed to *H. sapiens* (Haile-Selassie et al., 2004). In the Herto Member of the Bouri formation appear fossils, such as the cranium BOU-VP-16/1 (White et al., 2003), which were classified as *H. sapiens* by Tim White et al. The age of Herto specimens, obtained by $^{40}Ar/^{39}Ar$ method, is of 160–154 ka (Clark et al., 2003). From Singa (Sudan) came a calvarium found in 1924 and ascribed to *H. sapiens* (Rightmire, 1984) whose dating by mass-spectrometric U-Th is of 133 ± 2 ka (McDermott et al., 1996). Günther Bräuer et al. (1997) proposed that the oldest modern humans evidences would be a cranium (KNM-ER 3884) and a femur (KNM-ER 999) from Koobi Fora (Kenya), dated by uranium series, respectively, at 270 and 300 ka. Nevertheless, the most interesting fossils are the South African.

Along with its role in documenting cultural evolution—which we will see soon—South Africa has also provided evidence on the origin and dispersals of the first *H. sapiens*. Various sites from the most southerly part of South Africa, near Cape Town, such as Border cave (de Villiers, 1973), Klasies River Mouth (Singer and Wymer, 1982), Equus cave (Grine and Klein, 1985), Die Kelders cave, Blombos cave (Henshilwood et al., 2001), Sibudu (Backwell et al., 2008), Hofmeyr (Grine et al., 2007) and Hoedjiespunt (Berger and Parkington, 1995), among others, have provided the most important samples of the emergence of modern humans. The fossils from these sites are normally of lesser significance and of dubious dating. But the importance of the association between fossil specimens and archaeological remains in South Africa lies in the fact that the Khoe-San hunter-gatherers, the oldest living identified ethnicity, are found there. Their separation from the rest of human populations occurred at least 100,000 years ago (Schlebusch et al., 2012); thus, the age of our species should be older than that.

The evidence of an earlier division of *H. sapiens* populations reveals that the transit from Mode 3 to Mode 4 could not be deduced by comparison between the technological level of Neandertals and Cro-Magnon in the range of ≈40 ka. It must be found in the cultural development of *H. sapiens* in Africa, which took place at a time (100–200 ka) when the appearance and early evolution of our species occurred. A review of African cultural evolution of that period reveals the meaning of the proposed model of gradual change by McBrearty and Brooks (2000) to which we referred earlier.

THE AFRICAN MIDDLE STONE AGE

The traditional consideration of the African archaeological record was influenced by the scheme used to create the European sequence of Lower, Middle, and Upper Paleolithic stages. The cultural phases of Africa were consonantly grouped into Early, Middle, and Late Stone Age (ESA, MSA, and LSA, respectively). ESA encompasses not only Mode 1 but also Mode 2, so that the difference between the cultural level of ESA and MSA comes from innovations that go beyond the tools of the Acheulean culture. If ESA is linked especially with large bifaces (LFA hand axes), the MSA has been traditionally characterized by the absence of large bifaces, an emphasis on Levallois technology, and the presence of points (Goodwin and Van Riet Lowe, 1929).

Both East Africa as well as South Africa contain evidence of an ancient presence of MSA technocomplexes. In addition to the findings on the surface, whose age is imprecise, about 60 sites in East Africa susceptible to dating which contain MSA utensils (Basell, 2008) have been described. According to the review by Laura Basell (2008), their ages range from <200 ka to about 40 ka. The beginning of MSA could be even much older. Jayne Wilkins (2013) indicated that there are MSA utensils at Kathu Pan 1 site (Northern Cape, South Africa) of an age of up to ≈500 ka.

In principle, ESA and MSA could be distinguished simply by the presence of hand axes or points. But, as clarified by Sally McBrearty and Christian Tryon (2006), the sites normally lack tools capable of leading to a formal classification. The problem is that "formal tools are vastly outnumbered at nearly all sites by flakes, cores, and expedient tools, and the basic flake and core artifact inventories [of the Acheulean and MSA], are in many cases indistinguishable" (McBrearty and Tryon, 2006). In the absence of reliable dating, we face the fact that the method of direct percussion is not an accurate chronological marker. However, MSA can also be associated with "blade and microlithic technology, bone tools, increased geographic range, specialized hunting, the use of aquatic resources, long distance trade, systematic processing and use of pigment, and art and decoration" (McBrearty and Brooks, 2000). And among the innovations related to hunting are procedures and resources that were attributed initially to Mode 4 of European Cro-Magnon, as is the use of hafting adhesives, identified in the South African MSA (Charrié-Duhaut et al., 2013).

Considering the novelty of compound-adhesive manufacture, the age of the emergence of the oldest MSA is fixed at ≈300 ka (Henshilwood and Dubreuil, 2012; Wadley, 2010). Dates of that range are similar to those of the lower horizon of Gademotta formation (Ethiopia), 276 ± 4 ka (Morgan and Renne, 2008) and the Bedded Tuff Member

of Kapthurin formation (Kenya), 284 ± 24 ka (Deino and McBrearty, 2002), obtained both by $^{40}Ar/^{39}Ar$. However, as argued by Robert Foley et al. (2013) "The majority of MSA sites postdate 130 Ka, and it is from the beginning of MIS5 (≈130–74 Ka) and during MIS4 (74–60 Ka) that the classic African MSA becomes widespread and abundant."

South African sites have allowed the study in greater detail of the development of MSA, especially in its final stages, and the transition to LSA.

There are several concurrent processes at the temporal range of 80–60 ka: the expansion of modern human populations, their exit from Africa, and the emergence of technological and symbolic innovations associated with the modern mind. Naturally, the possibility of specifying dates, in particular for new tools, becomes the key to relate all those events. The final stages of cultural evolution within the MSA correspond in South Africa to the traditions of Still Bay (SB) and Howiesons Poort (HP), widespread in the southern cone of Africa. The study of Zenobia Jacobs et al. (2008) characterizes SB as flake-based technology, which includes finely shaped, bifacially worked, lanceolate points that were probably parts of spearheads. On the other hand, HP is described as "blade-rich … associated with backed (blunted) tools that most likely served as composite weapons, made of multiple stone artifacts." However, both traditions share "associated bone points and tools, engraved ochres and ostrich eggshells, and shell beads." Four South African sites are particularly useful to detail the scope of SB and HP phases: Diepkloof, Sibudu, Blombos, and Klasies River. The first two because they have tools of both traditions. Blombos, because the abundance of engravings, pigments, and perforated beads. Klasies River, because the fossil remains led to clarification of which hominins were responsible for the transition from MSA to LSA. This is something of special interest because both SB and HP already show different innovations which previously were associated only with the most advanced culture of the Upper Paleolithic.

Sibudu cave, located in KwaZulu-Natal North coasts, near Durban (South Africa), include a remarkable sequence of MSA occupations extending over a short timeframe. The first MSA tools which appeared in the Marine Isotope Stage (MIS) 4, ie, are older than ≈61 ka. From that point, phases follow one after another: pre-SB, SB, HP, post-HP, and late and final MSA phases directly overlain by Iron Age occupation (Backwell et al., 2008). The final phases, post-HP, of Sibudu have been studied by Manuel Will et al. (2014), attributing to MIS 3 around 58 ka. This proliferation of different traditions over a short period may have been related to both climate change as well as the tendencies of hunter-gatherers in regard to their use of local resources.

Diepkloof Rock Shelter shows a similar succession. It is located on the west coast of South Africa (Western Cape Province), 14 km from the Atlantic at the Table Mountain Group, very close to various sites with MSA industry. The excavation completed up to 2013 reveals the following sequence: MSA (type "Mike"); Pre-SB-SB-Early HP-MSA (type "Jack"); Interm. HP-Late HP-Post-HP (Porraz et al., 2013b). The change from SB-HP in Diepkloof is abrupt and that rapid shift has been interpreted in three ways: a population replacement, a discontinuity in the archaeological record, and/or a fast innovation, with a new way of hafting (and using) tools (Igreja and Porraz, 2013). However, Porraz et al. (2013b) disagree with the hypothesis connecting the appearance of the SB and the HP to the arrival of new populations. Instead, the authors support a scenario based on local evolution with distinct technological traditions that coexisted in South Africa during MIS 5. As argued by Porraz et al. (2013a), during MIS 5 there was "the coexistence of multiple, distinct technological traditions. We argue that the formation of regional identities in southern Africa would have favored and increased cultural interactions between groups at a local scale, providing a favorable context for the development and diffusion of innovations … The southern African data suggest that the history of modern humans has been characterized by multiple and independent evolutionary trajectories and that different paths and scenarios existed toward the adoption of 'modern' hunter-gatherer lifestyles." Within that independent evolution SB and HP traditions appear and disappear at the sites in very short periods. But on the whole these technocomplexes "are neither of short duration in time, nor homogeneous across space" (Porraz et al., 2013b). Consequently, for Porraz et al. (2013b), the traditions SB and HP cannot be considered as horizon markers.

THE PROTAGONISTS OF THE SOUTH AFRICAN MSA

Jayne Wilkins (2013) pointed out the general characteristics of the human evolution related to the development of MSA in South Africa. For this author the earlier MSA is "generally attributed to a group of hominins that are variably described as late archaic *H. sapiens*, or *H. helmei* [meanwhile] by ~195–150 ka, anatomically modern human fossils are known from East Africa … and modern *H. sapiens* are responsible for the later MSA" (Wilkins, 2013).

In a review article that overviews how the South African Pleistocene *Homo* fossil record correlates with the Stone Age sequence, Gerrit Dusseldorp et al. (2013) have argued about the basic problem to establish the correlation between fossils and tools: few South African hominin fossils can be placed between ≈200 ka and 110 ka, ie, during the probable dates of transformation from

Mid-Pleistocene *Homo* to modern *H. sapiens* in the region. With an age ranging between ≈110 and 40 ka, specimens appeared at Klasies River, such as jaws KRM 41,815 and 16,424 and the cranial fragments KRM 27,070 attributed to *H. sapiens*. From Border cave site came the jaw BC 5, with an accurate dating of 74 ± 5 ka, obtained by electronic spin resonance from a tooth fragment (Grün et al., 2003). In such a manner, 74,000 years would be the minimum age for the presence of *H. sapiens* in South Africa (a complete list of Early, Middle Pleistocene, and Modern *Homo* of South Africa is given in Dusseldorp et al., 2013, Supplementary material). The set of South African fossils, associated with MSA technocomplexes mainly belong to MIS 5 and MIS 4, and can be called "transitional." Its morphology is modern, but the process of gracilization, leading to the form and dimensions of contemporary populations, was not yet completed (Dusseldorp et al., 2013). As Dusseldorp et al. (2013) said: "On the whole, the fossil record from this period suggests that South Africa was occupied by populations showing a wide range of anatomical variation."

Between the end of MSA and the beginning of LSA, two complete fossils of modern morphology are available in South Africa: the Hofmeyr skull and the jaw of Bushman Rock Shelter. Both specimens are attributed to MIS 3, with an age for the child's jaw of Bushman Rock Shelter—assigned tentatively to site levels 16 or 17—of ≈29.5 ka (Protsch and de Villiers, 1974). The Hofmeyr skull has been dated at 36.2 ± 3.3 ka by thermoluminescence and uranium series. The phenetic affinities of the Hofmeyr skull were studied by Frederick Grine et al. (2007) using a multivariant analysis of linear measurements, as well as the coordinates of 19 three-dimensional points in comparison with those of modern humans from North Africa (Mesolithic), sub-Saharan Africa, West Eurasia, Oceania, and East Asia/New World, along with two Neandertals, four Upper Paleolithic modern humans, and one modern human from the Levant, also of Upper Paleolithic. The result of the analysis indicates that the anatomy of the Hofmeyr skull is closer to that of modern human populations from Eurasia of the Upper Pleistocene than to the current Khoe-San (Grine et al., 2007). This result supports, according to Grine et al. (2007), the hypothesis that early modern humans, which migrated to Eurasia, came from South Africa.

This anatomical connection, the presence of an advanced technology of tool making and the evidence of the emergence of what could be called modern behavior, in cognitive terms which go beyond the technological level, make South Africa a site of great value to understand the last steps of human evolution. In this respect Blombos site becomes important. Its human remains provide only a little information; during 1997−1998 campaigns, four teeth were found in Blombos cave, two of them deciduous teeth, some of which, with respect to the crown diameter, belong to the modern human range. But the peculiarity of Blombos is linked to the presence of ocher pieces.

The presence of red ocher—hematite (iron oxide)—is very common in all South African sites of the Late MSA, and stones with signs of use have striations which are attributed widely to the acquirement of powder for pigment making. In the absence of polychrome on the walls of caves, it is possible to infer that the use of the pigment is related to other symbolic behavior. As argued by Christopher Henshilwood et al. (2001), one intuitive conclusion, shared by most archaeologists, is that MSA ocher was used for body-paint/cosmetic and possibly the decoration of organic artifacts. But, in the absence of empirical evidence, that hypothesis is entirely speculative. Blombos' value lies in the contribution of evidence linking ocher and symbolism.

Blombos cave is located near the Indian Ocean, 25 -km west of SB town and 300 -km east of Cape Town. The site is located 100 m from the coast and at an elevation of 34.5 m above sea level. In Blombos MSA levels more than 8000 pieces of ocher have been found, many with signs of use (Henshilwood et al., 2002), among which the most outstanding are the geometric engravings, present in the three sedimentary phases of Blombos, thus, over nearly 100 ka (Henshilwood et al., 2009). As Henshilwood et al. (2009) pointed out, "The fact that they were created, that most of them are deliberate and were made with representational intent, strongly suggests they functioned as artefacts within a society where behavior was mediated by symbols." In other words, we find an empirical example of the "new mind." Blombos documents undoubtedly the presence of Mode 4.

THE WAY OUT OF AFRICA FOR *HOMO SAPIENS*

The process leading to modern humans, from their emergence and development of Mode 4 in Africa, to their entry into Europe, and to the "artistic explosion" that appears in the caves of Southern France and Northern Spain, is controversial. To clarify the ancestral genetic blueprint of current humans, Toomas Kivisild et al. (2006) conducted an analysis of the whole mtDNA of 277 individuals from five African haplogroups, L0 to L5. The most parsimonious cladogram obtained shows that the L0d, corresponding to Khoe-San people, is the ancestral subhaplogroup with respect to the rest of Africans. Recent analysis of single nucleotide polymorphisms (SNPs) in the nuclear DNA, supported the sub-Saharan origin of modern humans (Jakobsson et al., 2008; Li et al., 2008). The details of Khoe-San genetic variation have been offered by Carina Schlebusch et al. (2012) by genotyping ≈2.3 million SNPs in 220 South Africans. The results of the study indicated

that the divergence between the Khoe-San and other modern African humans took place more than 100,000 years ago—that is to say, near the very beginning of the emergence of *H. sapiens*—although the genetic distribution of the modern day Khoe-San goes back only about 35,000 years.

Paul Mellars (2006b) has proposed a model for the origin and dispersal of modern humans, which could be summarized in the following events:

- genetic evidence:
  - MIS 5 (130−80 ka)
    - Presence of *H. sapiens* in the Near East
    - Evolutionary changes in South Africa
  - MIS 4 (71−60)
    - Expansion to Africa
    - Dispersal to Eurasia
- Archaeological evidence
  - MIS 5
    - Emergence of the "modern mind" in South Africa
    - Dispersal to North Africa and the Near East
  - MIS 4
    - Dispersal of the "modern mind" into Eurasia

A key element of this model is formed by the episode of ≈65 ka ago, with a coastal dispersal of *H. sapiens* populations which took advantage of high-productivity areas of resources to expand into Asia until they reached the Wallacea and Sahul regions (Mellars et al., 2013). As Jane Balme et al. (2009) indicated, the occupation of diverse ecosystems with hostile environments and depressed fauna, could only have occurred with the use of complex systems of exchange and communication, including language. Although it is difficult to verify this hypothesis, what these authors argue is equivalent to an acceptance that Southeast Asian settlers in that time range possessed the modern mind.

Cultural evolution in Asia associates *H. sapiens* as the only species to which the cognitive traits of the modern mind can be attributed; however, the European case is different. If the southern and coastal dispersals of modern humans into Asia took place c. 65−60 ka ago, the dispersal permitting the occupation of Europe by the Cro-Magnon is later: 47−41 ka, according to data calibrated by radiocarbon (Mellars, 2006a). Cultural traditions commonly attributed to modern humans entering Europe are, cited in order of antiquity, the industries Aurignacian, Gravettian, Solutrean, and Magdalenian.

The Aurignacian culture was defined by Edouard Lartet (1860) in accordance with the tools found at the site of Aurignac (French Pyrenees), but is also assigned to similar industry sets from large parts of Eastern, Western, and Central Europe, and also to some of the existing technocomplexes in parts of the Middle East (Mellars, 2006a). The technological level of Aurignacian contrasts with the Mousterian Mode 3 of Neandertals. The most obvious difference is the use of microbladelet technology, representing a major difference from the most advanced tools up to that time. If Châtelperronian points, as well as bladelets, fulfill the same purpose, to serve as projectiles, the Aurignacian microliths are "serially, laterally hafted along the shaft of projectiles, not mounted at their extremities" (Bon, 2006).

The need to compare the technocomplexes of Mode 3 and Aurignacian led to distinguish the latter as belonging to a homogeneous tradition, following the initial descriptions such as those by Abbe Breuil (1913). However, technological analysis determined the presence of different forms of tool production in the Aurignacian. For the initial carvings, in contrast with Mode 3, several different names were proposed—"Classic Aurignacian," "Aurignacian I," "Proto-Aurignacian," "Early Aurignacian," "Pre-Aurignacian," "Archaic Aurignacian," "Initial Aurignacian"—and applied to techniques that in some instances are quite similar. Some authors have even suggested that between the initial carvings of Mode 4 and the most advanced Aurignacian there are very few differences (Nejman, 2008). However, François Bon (2006) has argued that, from a technological point of view, two different systems can be distinguished, which the author called "Archaic (or Proto) Aurignacian" and "Early Aurignacian." The difference consists in that only one *chaîne opératoire* is required to obtain Archaic Aurignacian tools, meanwhile two distinct *chaînes opératoires* are required to obtain blades and bladelets of the Early Aurignacian (Bon, 2006). As William Banks et al. (2013) stated, "For the Proto-Aurignacian, blades and bladelets were produced from unidirectional prismatic cores within a single, continuous reduction sequence … During the Early Aurignacian, blades and bladelets were produced via two distinct core reduction strategies. Blades continued to be produced from prismatic cores, were robust, and were typically heavily retouched on their lateral edges. Carinated 'scrapers' served as specialized cores whose reduction yielded short, straight, or curved bladelets that were typically left unretouched. The Early Aurignacian is also characterized by the appearance of split-based bone points." (Banks et al., 2013).

The oldest documented presence of Archaic or Proto-Aurignacian is found before the cold Heinrich Event 4 (HE4) (≈40 ka) in Northern Spain (El Castillo, Cantabria, level 18, 41−38 ka; l'Arbreda, Catalonia, level 11, 41−39 ka) and Northern Italy (Paina 38.6−37.9; Fumane 36.8−32.1) (Kozlowski and Otte, 2000), Southern France (Isturitz 37.18 ± 4.2 ka (Szmidt et al., 2010)), and Moravia (Brno-Bohunice, ≈48 ka (Hoffecker, 2009)). The oldest evidence of the Early Aurignacian would be of almost 34 ka in France (Castanet Lower, Combe Saunière VIII,

Flageolet I XI, Pataud 11 and 13, Roc de Combe 7c, Tuto de Camalhot 70e8) and Germany (Geissenklösterle IIIa, Wildscheuer III) (Banks et al., 2013). The lowest strata of Hohle Fels cave, which ranged between 36 and 33 ka, contains ivory sculptures in addition to facies of Early Aurignacian (Conard, 2003). Banks et al. (2013, Table 44.2) give radiocarbon calibrated dates associated with the Proto-Aurignacian and Early Aurignacian in Europe.

The biggest obstacle to give meaning to the Archaic and Early Aurignacian cultures is the absence of associated fossils. Therefore, as stated by Joao Zilhao (2006), these industries can be attributed to both Neandertals and modern humans. We have, then, a problem for the identification of the "modern mind." If we associate it to the technological level of cultures immediately preceding the advanced Aurignacian, Neandertals could also have had that cognitive capacity. But, if we relate the modern mind with realistic representations of figurative cave art, these only appear at the end of the Aurignacian. Early modern humans would then have lacked such a capacity.

TRANSITIONAL INDUSTRIES

The meaning of the emergence of the modern mind in both technological and symbolic terms becomes clearer by analyzing the transitional industries. According to Ivor Jankovic et al. (2006), these "include the Châtelperronian of France and northern Spain, Szeletian and Jankovichian of central and parts of eastern Europe, Uluzzian of Italy (Tuscany, Calabria, southern Adriatic part, Uluzzo Bay, etc.), Streletskian of eastern Europe, Jerzmanowician of eastern Germany and Poland, Althmulian of southern Germany, Bohunician of Czech Republic, Brynzeny and Kostenki Szeletian of Russia and several other unnamed or site-specific assemblages from Poland, Slovakia, Czech Republic, Romania, etc." They are called "transitional" because they contain elements of the Middle Paleolithic (Mousterian, Micoquian), absent in the Early Aurignacian, such as curved-backed points and foliate points (Kozlowski and Otte, 2000), but also tools that are considered characteristic of the Upper Paleolithic, such as carinated scrapers or bone points. David Brose and Milford Wolpoff (1971, Table 44.1) provide a long list of Upper Paleolithic utensils found in Middle Paleolithic contexts.

The problem of the transitional industries appears when we need to assign them to a species. As was indicated by Jankovic et al. (2011), "even if we accept the earliest Aurignacian as an industrial complex that has its origins outside this area … (which is far from proven) and attribute it to anatomically modern newcomers (for which there are no known hominin/ industrial associations) we are left with the problem of who is responsible for these Initial Upper Paleolithic assemblages." The absence of fossil remains associated with almost every transitional technocomplex generally prevents the association of hominin/industry, and of confirming who were the architects of this cultural change. However, two sites with Châtelperronian culture, Saint-Césaire (c. 36 ka) (Lévêque and Vandermeersch, 1980; Mercier et al., 1991) and Arcy-sur-Cure (c. 34 ka) (Hublin et al., 1996), contain in the same stratigraphic level fossils of *H. neanderthalensis* (questioned by Bar-Yosef and Bordes, 2010; Higham et al., 2010). This coincidence has been at times enough to attribute all transitional industries to Neandertals (Allsworth-Jones, 1986; Mellars, 1996; Stringer and Gamble, 1993); a consideration sustained in some revisions of specialists (Churchill and Smith, 2000; Francesco d'Errico, 2003).

The general assignment of transitional industries to the Neandertals encounters the problem of the morphology of fossil specimens found at Uluzzian levels. In the Grotta di Fumane (Lessini Mountains, North Italy) several human teeth have been found: Fumane, 1, 4, 5, deciduous; Fumane 6, adult. Stefano Benazzi et al. (2014) classified Fumane 1 as clearly Neandertal, and Fumane 5 as supporting Neandertal affinity. Both specimens come from the Mousterian levels of Fumane. At the same time, Fumane 6, of the Uluzzian levels, does not show morphological features useful for taxonomic discrimination (Benazzi et al., 2014). Fumane fossil specimens, therefore, do not contradict the general attribution of Uluzzian to Neandertals. However, a new analysis by Stefano Benazzi et al. (2011) of two deciduous molars from the Uluzzian levels (EIII) of the Grotta del Cavallo (Apulia, Southern Italy), one initially classified as a Neandertal, leads to different conclusions. By means of morphometric methods based on microtomographic data, Benazzi et al. (2011) stated that the Cavallo specimens can be attributed to modern humans. In addition, in the EIII level of the Grotta del Cavallo appeared several marine shells (*Dentalium* sp., *Nuculana* sp., and *Cyclope neritea*) snapped or pierced to be transformed into beads.

If the Uluzzian technocomplex, very ancient, is the production of modern humans, we find ourselves with the possibility to establish plausible dates for the entry into Europe of *H. sapiens*. The Grotta di Fumane (Lessini Mountains, North Italy) contains levels of the late Mousterian (A11, A5), Uluzzian (A4, A3), and Proto-Aurignacian (A2, A1 up to D3) technocomplex (Benazzi et al., 2014). Fumane Mousterian levels were dated by calibrated radiocarbon between 45.4 and 41.7 (A11) and 38.875 ± 1.497 ka (A5), while the Uluzzian level (A4) received 37.8–36.9 ka (Peresani et al., 2008). Applying a development of radiocarbon dating (acid-base-oxidation-stepped combustion—ABOx-SC—and acid-base-acid—ABA—pretreatments for removing contaminants, then accelerator mass spectrometry—AMS), Thomas Higham et al. (2009) increased the age of the fossils of Cavallo. The age of the Proto-Aurignacian A2 level would be

41.20−40.45 ka, ie, prior to the Campanian Ignimbrite eruption. The latest Mousterian occupation (A5) would be 43.58−42.98 ka, and the Uluzzian levels should be found between that date and 41.20−40.45 ka. The analysis by Katerina Douka et al. (2014) pushed back even further the age of the Uluzzian. By an integrated synthesis of new radiocarbon results and a Bayesian statistical approach from four stratified Uluzzian cave sequences in Italy and Greece (Cavallo, Fumane, Castelcivita, and Klissoura 1), Douka et al. (2014) concluded that the Uluzzian arrived in Italy and Greece shortly before 45 ka. Its final stages are ≈39.5 ka, coinciding with the Campanian Ignimbrite eruption. Fumane dates agree with that of the Grotta del Cavallo. Benazzi et al. (2011) dated the Cavallo shells by AMS radiocarbon at an age of 45.01−43.38 ka.

The latest scenario presents, therefore, the arrival of Uluzzian technocomplexes—ie, of modern humans—in Italy and Greece, with the modern mind necessary to use personal ornaments (beads), shortly before 45 ka, a date old enough to match the Châtelperronian levels of Neandertals in France and northern Spain. Additionally, beads and ocher pigments also appear at the Châtelperronian sites. The Grotte du Renne, Arcy-sur-Cure (France), a site inhabited by Neandertals (Hublin et al., 1996), in addition to Châtelperronian tools constructed in situ has yielded a series of up to 36 objects such as carved ivory pieces and perforated bones, the sole purpose of which must have been decorative. In addition to Châtelperronian tools constructed in situ, the Grotte du Renne (Arcy-sur-Cure, France) has yielded a series of up to 36 objects such as carved ivory pieces and perforated bones, the sole purpose of which must have been decorative (Hublin et al., 1996). Since 1949 Leroi-Gourhan carried out studies that revealed important differences between the engraving techniques used to produce the Arcy-sur-Cure Châtelperronian artifacts and the latest Aurignacian utensils that were found in the most modern strata of the same cave (Leroi-Gourhan, 1958, 1961). Hence, the Châtelperronian (Neandertal) and Aurignacian (modern human) cultures were different. But the decorative objects from the Grotte du Renne raised doubts about these differences existing between modern humans and Neandertals. Thus, Hublin et al. (1996) interpreted the Arcy-sur-Cure artifacts as the result of trading process rather than the result of technical imitation of modern human technology. Francesco d'Errico et al. (1998) arrived at a different conclusion: those objects were the result of an independent and characteristically Neandertal cultural development, which had managed to cross the threshold of the symbolism inherent in decorative objects. There is no reason to assume that the biological differences between Neandertals and modern humans necessarily translated into differences between their intellectual capacities. Paul Bahn (1998) also believed the Arcy-sur-Cure objects merited attributing Neandertals a sophisticated and modern symbolic behavior.

Randall White (2001) has offered an alternative interpretation of the decorative objects from the Grotte du Renne: "It seems implausible that … Neandertals and Cro-Magnons independently and simultaneously invented personal ornaments manufactured from the same raw materials and using precisely the same techniques." Consequently, he argues that the Châtelperronian ornaments from the Grotte du Renne are Aurignacian and were produced by modern humans. The question whether the authors of the Châtelperronian culture were Neandertals, modern humans, or both, has sparked numerous discussions. The evidence from Saint-Césaire (France), with both Middle and Upper Paleolithic strata, allowed in situ studies of the association of specimens and tools, as well as the cultural transition (Mercier et al., 1991). Norbert Mercier et al. (1991) used thermoluminescence to estimate the age of the Neandertal specimens found in levels with Châtelperronian industry. Their results suggest they were 36,300 ± 2700 years old. Mercier et al. (1991) argued that there was contact between Neandertals from Western Europe and the first modern humans that arrived there. They also noted something we have said on several occasions: the straightforward identification of cultures with taxa is not possible.

Arcy-sur-Cure suggests Neandertals were possibly capable of producing decorative objects; other sites provide evidences of cultural sharing. Ivor Karavanic and Fred Smith (1998) documented the presence of two contemporary sites at Hrvatsko Zagorje (Croatia) which are close to each other. The Vindija cave has yielded Neandertals, while Velika Pécina has only produced remains of anatomically modern humans. The authors believed that the coincidences exhibited by the tools from both sites are due to imitation or even commercial exchange. These Croatian sites do not include ornaments, but they provide remarkable indications of cultural exchange. This is corroborated beyond a doubt by *H. neanderthalensis* and *H. sapiens* coincident at Palestine caves. Although the shared Near East Mousterian culture could be interpreted as the maximum horizon Neandertals could reach, the Arcy-sur-Cure objects, assuming they were constructed or used by Neandertals, suggest this was not the case. They seem to support the notion that Neandertals appreciated pendants enough to identify them as "beautiful objects." At least in this sense, they would have achieved the "modern mind."

The hypothesis that Neandertal decorative elements found in the Châtelperronian deposits are imitations of Aurignacian objects made by modern humans implies that both cultures were contemporary or that the Aurignacian culture was older. Joao Zilhão et al. (2006) have investigated the sequence of sediments and the archaeological association of the Grotte des Fées at Châtelperron (France) and reject the Châtelperronian-Aurignacian

contemporaneity: They assert that "its stratification is poor and unclear, the bone assemblage is carnivore accumulated, the putative interstratified Aurignacian lens in level B4 is made up for the most part of Châtelperronian material, the upper part of the sequence is entirely disturbed, and the few Aurignacian items in levels B4–5 represent isolated intrusions into otherwise in situ Châtelperronian deposits" (Zilhão et al., 2006). Their conclusion is that "as elsewhere in southwestern Europe, this evidence confirms that the Aurignacian postdates the Châtelperronian and that the latter's cultural innovations are better explained as the Neandertals' independent development of behavioral modernity" (Zilhão et al., 2006). This hypothesis deserves attention, but to be accepted similar studies should be carried out at places other than the Grotte des Fées.

Any chronological table of the cultural sequences reveals the difficulties we are encountering. Direct correspondences are usually drawn between cultural manifestations and species, associating Mousterian with Neandertals and Aurignacian with modern humans. Hence, it seems clear that attributing or not to Neandertals sufficient cognitive capacities for aesthetic experience is heavily influenced by a given author's point of view about the Mousterian evidence. Those who argue that Neandertals and *H. sapiens* belong to different species tend to reject the presence of the "modern mind" in the former's contrivances, and vice versa.

REFERENCES

Abbate, E., Albianelli, A., Azzaroli, A., et al., 1998. A one-million-year-old *Homo* cranium from the Danakil (Afar) depression of Eritrea. Nature 393, 458–460.

Akazawa, T., Muhesen, M., Dodo, Y., et al., 1995. Neanderthal infant burial. Nature 377, 585–586.

Allsworth-Jones, P., 1986. The Szeletian and the Transition from Middle to Upper Paleolithic in Central Europe. Oxford University Press, Oxford.

Ambrose, S.H., 2001. Paleolithic technology and human evolution. Science 291, 1748–1753.

Asfaw, B., Beyene, Y., Suwa, G., et al., 1992. The earliest Acheulan from Konso-Gardula. Nature 360, 732–735.

Backwell, L., d'Errico, F., Wadley, L., 2008. Middle stone age bone tools from the Howiesons Poort layers, Sibudu Cave, South Africa. Journal of Archaeological Science 35 (6), 1566–1580.

Bahn, P.G., 1998. Neanderthals emancipated. Nature 394, 719–720.

Balme, J., Davidson, I., McDonald, J., et al., 2009. Symbolic behaviour and the peopling of the southern arc route to Australia. Quaternary International 202, 59–68.

Banks, W.E., d'Errico, F., Zilhão, J., 2013. Human-climate interaction during the early upper Paleolithic: testing the hypothesis of an adaptive shift between the proto-Aurignacian and the early Aurignacian. Journal of Human Evolution 64 (1), 39–55.

Bar-Yosef, O., Belmaker, M., 2011. Early and middle pleistocene faunal and hominins dispersals through southwestern Asia. Quaternary Science Reviews 30 (11–12), 1318–1337.

Bar-Yosef, O., Bordes, J.-G., 2010. Who were the makers of the Châtelperronian culture? Journal of Human Evolution 59 (5), 586–593.

Bar-Yosef, O., Vandermeersch, B., 1993. Modern humans in the levant. Scientific American 268 (4), 94–100.

Basell, L.S., 2008. Middle Stone Age (MSA) site distributions in eastern Africa and their relationship to Quaternary environmental change, refugia and the evolution of *Homo sapiens*. Quaternary Science Reviews 27 (27–28), 2484–2498.

Belmaker, M., Tchernov, E., Condemi, S., et al., 2002. New evidence for hominid presence in the lower pleistocene of the southern levant. Journal of Human Evolution 43 (1), 43–56.

Benazzi, S., Bailey, S.E., Peresani, M., et al., 2014. Middle Paleolithic and Uluzzian human remains from Fumane cave, Italy. Journal of Human Evolution 70, 61–68.

Benazzi, S., Douka, K., Fornai, C., et al., 2011. Early dispersal of modern humans in Europe and implications for Neanderthal behaviour. Nature 479 (7374), 525–528.

Berger, L.R., Clarke, R.J., 1996. The Load of the Taung child. Nature 379, 778–779.

Berger, L.R., Parkington, J.E., 1995. A new Pleistocene hominid-bearing locality at Hoedjiespunt, South Africa. American Journal of Physical Anthropology 98, 601–609.

Binford, L.R., 1981. Bones: Ancient Men and Modern Myths. Academic Press, New York.

Blumenschine, R., 1987. Characteristics of an early hominid scavenging Niche. Current Anthropology 28, 383–408.

Boesch, C., Head, J., Robbins, M.M., 2009. Complex tool sets for honey extraction among chimpanzees in Loango National Park, Gabon. Journal of Human Evolution 56, 560–569.

Boesch, C., Tomasello, M., 1998. Chimpanzee and human cultures. Current Anthropology 39, 591–595.

Bon, F., 2006. A brief overview of Aurignacian cultures in the context of the industries of the transition from the Middle to the Upper Paleolithic. In: Bar Yosef, O., Zilhão, J. (Eds.), Towards a Definition of the Aurignacian. American School of Prehistoric Research/Instituto Português de Arqueologia, Lisbon, pp. 133–144.

Bordes, F., 1953. Nodules de typologie paléolithique I. Outils musteriens à fracture volontaire, vol. 1. Bulletin de la Societé Préhistorique Française, Paris, p. 50.

Bordes, F., 1979. Typologie du Paléolithique ancien et moyen, vol. 1. CNRS, Paris.

Bouyssonie, A., Bouyssonie, J., Bardon, L., 1908. Découverte d'un squelette humain mousterian à la bouffia de la Chapelle-aux-Saints (Corrèze). L'Anthropologie 19, 513–519.

Brain, C.K., 1958. The Transvaal ape-man bearing cave deposits. Transvaal Museum Memoir 11, 1–125.

Brain, C.K., 1970. New finds at the Swartranks site. Nature 225, 1112–1119.

Bräuer, G., Yokoyama, Y., Falguères, C., et al., 1997. Modern human origins backdated. Nature 386, 337.

Breuil, H., 1913. Les subdivisions du Paléolithique supérieur et leur signification. In: Paper presented at the Congrès International d'Anthropologie et d'Archéologie préhistoriques. Compte-rendu de la 14ème session, Genève 1912, tome 1, Genève.

Brooks, A.S., Helgren, D.M., Cramer, J.S., et al., 1995. Dating and context of three middle stone age sites with bone points in the upper Semliki Valley, Zaire. Science 268, 553–556.

Brose, D.S., Wolpoff, M.H., 1971. Early upper Paleolithic man and late middle Paleolithic tools. American Anthropologist 73, 1156–1194.

Bunn, H.T., 1981. Archaeological evidence for meat-eating by Plio-pleistocene hominids from Koobi Fora and Olduvai gorge. Nature 291, 574–577.

Bye, B.A., Brown, F.H., Cerling, T.E., et al., 1987. Increased age estimate for the lower Paleolithic hominid site at Olorgesailie, Kenya. Nature 329, 237–239.

Callaway, E., 2015. Oldest stone tools raise questions about their creators. Nature 520, 421.

Cann, R.L., Stoneking, M., Wilson, A.C., 1987. Mitochondrial DNA and human evolution. Nature 325, 31–36.

Carbonell, E., Bermudez de Castro, J.M., Arsuaga, J.L., et al., 2005. An early pleistocene hominin mandible from Atapuerca-TD6, Spain. Proceedings of the National Academy of Sciences of the United States of America 102 (16), 5674–5678.

Carbonell, E., Mosquera, M., Rodríguez, X.P., 2007. The emergence of technology: a cultural step or long-term evolution? Comptes Rendus Palevol 6 (3), 231–233.

Charrié-Duhaut, A., Porraz, G., Cartwright, C.R., et al., 2013. First molecular identification of a hafting adhesive in the late Howiesons Poort at Diepkloof rock shelter (western Cape, South Africa). Journal of Archaeological Science 40 (9), 3506–3518.

Chauhan, P.R., 2010. Comment on 'Lower and Early Middle Pleistocene Acheulian in the Indian sub-continent' by Gaillard et al. (2009) (Quaternary International). Quaternary International 223–224, 248–259. http://dx.doi.org/10.1016/j.quaint.2010.01.021.

Churchill, S.E., Smith, F.H., 2000. Makers of the early Aurignacian of Europe. American Journal of Physical Anthropology 113 (Suppl. 31), 61–115.

Clark, G.A., 1969. World Prehistory: A New Synthesis. Cambridge University Press, Cambridge.

Clark, G.A., 1997. The middle-upper Paleolithic transition in Europe: an American Perspective. Norwegian Archaeological Review 30, 25–53.

Clark, J.D., Beyene, Y., WoldeGabriel, G., et al., 2003. Stratigraphic, chronological and behavioural contexts of pleistocene *Homo sapiens* from middle Awash, Ethiopia. Nature 423 (6941), 747–752.

Clark, J.D., Heinzelin, J., Schick, K.D., et al., 1994. African *Homo erectus*: old radiometric ages and Young Oldowan assemblages in the middle Awash valley, Ethiopia. Science 264, 1907–1920.

Clark, J.D., Kurashina, H., 1979. Hominid occupation of the east-Central Highlands of Ethiopia in the Plio-pleistocene. Nature 282, 33–39.

Clarke, R.J., Howell, F.C., Brain, C.K., 1970. More evidence of an advanced hominid at Swartranks. Nature 225, 1219–1222.

Conard, N.J., 2003. Palaeolithic ivory sculptures from southwestern Germany and the origins of figurative art. Nature 426 (6968), 830–832.

Curnoe, D., 2010. A review of early *Homo* in southern Africa focusing on cranial, mandibular and dental remains, with the description of a new species (*Homo gautengensis* sp. nov.). HOMO – Journal of Comparative Human Biology 61 (3), 151–177. http://dx.doi.org/10.1016/j.jchb.2010.04.002.

d'Errico, F., 2003. The invisible frontier. A multiple species model for the origin of behavioral modernity. Evolutionary Anthropology 12, 188–202.

d'Errico, F., Backwell, L., 2009. Assessing the function of early hominin bone tools. Journal of Archaeological Science 36 (8), 1764–1773. http://dx.doi.org/10.1016/j.jas.2009.04.005.

d'Errico, F., Backwell, L.R., 2003. Possible evidence of bone tool shaping by Swartkrans early hominids. Journal of Archaeological Science 30 (12), 1559–1576. http://dx.doi.org/10.1016/s0305-4403(03)00052-9.

d'Errico, F., Zilhão, J., Julien, M., Baffier, D., Pelegrin, J., 1998. Neanderthal acculturation in western Europe? A critical review of the evidence and its interpretation. Current Anthropology 39 (S1), S1–S44.

Dart, R.A., 1957. The Osteodontokeratic Culture of Australopithecus Prometheus (Pretoria).

Davidson, I., McGrew, W.C., 2005. Stone tools and the uniqueness of human culture. Journal of Royal Anthropological Institute 11, 793–817.

Day, M.H., 1986. Guide to Fossil Man, fourth ed. The University of Chicago Press, Chicago.

de Heinzelin, J., Clark, J.D., White, T., et al., 1999. Environment and behavior of 2.5-million-year-old Bouri hominids. Science 284, 625–629.

de la Torre, I., Mora, R., Martínez-Moreno, J., 2008. The early Acheulean in Peninj (Lake Natron, Tanzania). Journal of Anthropological Archaeology 27 (2), 244–264. http://dx.doi.org/10.1016/j.jaa.2007.12.001.

de Villiers, H., 1973. Human skeletal remains from border cave, Ingwavumu District, KwaZulu, South Africa. Annals of the Transvaal Museum 28, 229–256.

Deino, A., McBrearty, S., 2002. $^{40}Ar/^{39}Ar$ chronology for the Kapthurin formation, Baringo, Kenya. Journal of Human Evolution 42, 185–210.

Domínguez-Rodrigo, M., Barba, R., Egeland, C.P., 2007. Deconstructing Olduvai: A Taphonomic Study of the Bed I Sites. Springer, Dordrecht.

Dominguez-Rodrigo, M., Serrallonga, J., Juan-Tresserras, J., et al., 2001. Woodworking activities by early humans: a plant residue analysis on Acheulian stone tools from Peninj (Tanzania). Journal of Human Evolution 40, 289–299.

Douka, K., Higham, T.F.G., Wood, R., et al., 2014. On the chronology of the Uluzzian. Journal of Human Evolution 68, 1–13.

Dubois, E., 1894. Pithecanthropus erectus. Eine menschanähnliche Übergangsform aus Java. Landsdruckerei, Batavia.

Dusseldorp, G., Lombard, M., Wurz, S., 2013. Pleistocene *Homo* and the updated stone age sequence of South Africa. South African Journal of Science (5/6), 1–7.

Evernden, J.F., Curtiss, G.H., 1965. Potassium argon dating of late Cenozoic rocks in East Africa and Italy. Current Anthropology 6, 348–385.

Ferring, R., Oms, O., Agustí, J., et al., 2011. Earliest human occupations at Dmanisi (Georgian Caucasus) dated to 1.85–1.78 Ma. Proceedings of the National Academy of Sciences of the United States of America 108, 10432–10436.

Foley, R.A., Maíllo-Fernández, J.M., Mirazón Lahr, M., 2013. The Middle Stone Age of the Central Sahara: Biogeographical opportunities and technological strategies in later human evolution. Quaternary International 300, 153–170.

Gabunia, L., Vekua, A., 1995. A Plio-pleistocene hominid from Dmanisi, east Georgia, Caucasus. Nature 373, 509–512.

Gabunia, L., Vekua, A., Lordkipanidze, D., 2000. The environmental contexts of early human occupation of Georgia (Transcaucasia). Journal of Human Evolution 38 (6), 785–802.

Gabunia, L., de Lumley, M.A., Vekua, A., Lordkipanidze, D., de Lumley, H., 2002. Découverte d'un nouvel hominidé à Dmanissi (Transcaucasie, Géorgie). Comptes Rendus Palevol I, pp. 243–253.

Gargett, R., 1989. Grave shortcoming: the evidence for neandertal burial (commentary). Current Anthropology 30, 157–180.

Goodall, J.M., 1964. Tool-using and aimed throwing in a community of free-living chimpanzees. Nature 201, 1264–1266.

Goodwin, A.J.H., Van Riet Lowe, C., 1929. The Stone Age Cultures of South Africa, vol. 27. Annals of the South African Museum, Cape Town.

Grine, F.E., Bailey, R.M., Harvati, K., et al., 2007. Late pleistocene human skull from Hofmeyr, South Africa, and modern human origins. Science 315 (5809), 226–229.

Grine, F.E., Klein, R.G., 1985. Pleistocene and Holocene human remains from Equus Cave, South Africa. Anthropology 8, 55–98.

Groves, C.P., Mazák, V., 1975. An approach to the taxonomy of the Hominidae: Gracile Villafranchian hominids of Africa. Casopis pro Mineralogii a Geologii 20, 225–247.

Grün, R., Beaumont, P., Tobias, P.V., et al., 2003. On the age of Border Cave 5 human mandible. Journal of Human Evolution 45 (2), 155–167.

Haile-Selassie, Y., Asfaw, B., White, T.D., 2004. Hominid cranial remains from upper pleistocene deposits at Aduma, Middle Awash, Ethiopia. American Journal of Physical Anthropology 123 (1), 1–10.

Hedenström, A., 1995. Lifting the Taung's child. Nature 378, 670.

Henry-Gambier, D., 2002. Les fosssiles de Cro-Magnon (Les Eyzies-de-tayac, Dordogne): Nouvelles données sur leur position chronologique et leur attribution culturelle. Bulletins et Mémoires de la Société d'Anthropologie de Paris 14 (1–2), 89–112.

Henshilwood, C.S., d'Errico, F., Watts, I., 2009. Engraved ochres from the middle stone age levels at Blombos cave, South Africa. Journal of Human Evolution 57 (1), 27–47.

Henshilwood, C.S., d'Errico, F., Yates, R., et al., 2002. Emergence of modern human behavior: middle stone age engravings from South Africa. Science. http://www.sciencexpress.org/10 January 2002/Page 4/10.1126/science.1067575.

Henshilwood, C.S., Dubreuil, B., 2012. Style, symbolism, and complex technology: the middle stone age in southern Africa: a response to Shea. Current Anthropology 53 (1), 132–133.

Henshilwood, C.S., Sealy, J.C., Yates, R., et al., 2001. Blombos cave, southern Cape, South Africa: Preliminary report on the 1992, Äì1999 excavations of the middle stone age levels. Journal of Archaeological Science 28 (4), 421–448.

Higham, T., Brock, F., Peresani, M., et al., 2009. Problems with radiocarbon dating the middle to upper palaeolithic transition in Italy. Quaternary Science Reviews 28 (13–14), 1257–1267.

Higham, T., Jacobi, R., Julien, M., et al., 2010. Chronology of the Grotte du Renne (France) and implications for the context of ornaments and human remains within the Châtelperronian. Proceedings of the National Academy of Sciences of the United States of America 107, 20234–20239.

Hoffecker, J.F., 2009. The spread of modern humans in Europe. Proceedings of the National Academy of Sciences of the United States of America 106, 16040–16045.

Howell, F.C., 1952. Pleistocene glacial ecology and the evolution of 'classic neanderthal' man. Southwestern Journal of Anthropology 8, 377–410.

Hublin, J.J., Spoor, F., Braun, M., Zonneveld, F., Condemi, S., 1996. A late neanderthal associated with upper Palaeolithic artefacts. Nature 381, 224–226.

Igreja, M., Porraz, G., 2013. Functional insights into the innovative early Howiesons Poort technology at Diepkloof rock shelter (western Cape, South Africa). Journal of Archaeological Science 40 (9), 3475–3491.

Isaac, G.L., 1969. Studies of early cultures in East Africa. World Archaeology 1, 1–28.

Isaac, G.L., 1975. Stratigraphy and cultural patterns in East Africa during the middle ranges of Pleistocene time. In: Butzer, K.W., Isaac, G.L. (Eds.), After the Australopithecines. Mouton, The Hague, pp. 495–542.

Isaac, G.L., 1978. The archaeological evidence for the activities of early African hominids. In: Jolly, C.J. (Ed.), Early Hominids of Africa. Duckworth, London, pp. 219–254.

Isaac, G.L., 1984. The archaeology of human origins: studies of the Lower Pleistocene in Africa. In: Wendorf, F., Close, A. (Eds.), Advances in World Archaelogy, vol. 3. Academic Press, New York, pp. 1–87.

Jacobs, Z., Roberts, R.G., Galbraith, R.F., et al., 2008. Ages for the middle stone age of southern Africa: implications for human behavior and dispersal. Science 322 (5902), 733–735.

Jakobsson, M., Scholz, S.W., Scheet, P., et al., 2008. Genotype, haplotype and copy-number variation in worldwide human populations. Nature 451 (7181), 998–1003.

Jankovic, I., Karavanic, I., Ahern, J.C.M., et al., 2006. Vindija cave and the modern human peopling of Europe. Collegium Antropologicum 30, 457–466.

Jankovic, I., Karavanic, I., Ahern, J.C.M., et al., 2011. Archaeological, paleontological and genomic perspectives on late European Neandertals at Vindija cave, Croatia. In: Condemi, S., Weniger, G.-C. (Eds.), Continuity and Discontinuity in the Peopling of Europe: One Hundred Fifty Years of Neanderthal Study. Springer Science + -Business Media B.V, Dordrecht, pp. 299–313.

Karavanic, I., Smith, F.H., 1998. The Middle/Upper Paleolithic interface and the relationship of Neanderthals and early modern humans in Hrvatsko Zagorje, Croatia. Journal of Human Evolution 34, 223–248.

Kimbel, W.H., Walter, R.C., Johanson, D.C., et al., 1996. Late Pliocene *Homo* and Oldowan tools from the hadar formation (Kada hadar member), Ethiopia. Journal of Human Evolution 31, 549–561.

Kingston, J.D., Marino, B.D., Hill, A., 1994. Isotopic evidence for Neogene hominid Paleoenvironments in the Kenia Rift valley. Science 264, 955–959.

Kivisild, T., Shen, P., Wall, D.P., et al., 2006. The role of selection in the evolution of human mitochondrial genomes. Genetics 172 (1), 373–387.

Kozlowski, J.K., Otte, M., 2000. The formation of the Aurignacian in Europe. Journal of Anthropological Research 56 (4), 513–534.

Kuman, K., 2007. The earlier stone age in South Africa: site context and the influence of cave studies. In: Pickering, T.R., Schick, K., Toth, N. (Eds.), Breathing Life into Fossils. Stone Age Institute Press, Gosport, IN, pp. 181–198.

Lartet, E., 1860. Mémoire sur la station humaine d'Aurignac. ASNZ 15, 177–253.

Lartet, E., Christy, H., 1865–1875. Reliquiae Aquitanicae. Williams & Norgate, London.

Leakey, L.S.B., 1951. Olduvai Gorge. A Report on the Evolution of the Handaxe Culture in Beds I-IV. Cambridge University Press, Cambridge.

Leakey, L.S.B., Tobias, P.V., Napier, J.R., 1964. A new species of the genus *Homo* from Olduvai. Nature 202, 7–9.

Leakey, M., 1966. A review of the Oldowan culture from Olduvai gorge, Tanzania. Nature 212, 577–581.

Leakey, M.D., 1975. Cultural patterns in the Olduvai sequence. In: Butzer, K.W., Isaac, G.L. (Eds.), After the Australopithecines. Mouton, The Hague, pp. 477–493.

Leakey, M.G., Feibel, C.S., McDougall, I., et al., 1995. New four-million-year-old hominid species from Kanapoi and Allia Bay, Kenya. Nature 376, 565–572.

Lepre, C.J., Roche, H., Kent, D.V., et al., 2011. An earlier origin for the Acheulian. Nature 477 (7362), 82–85.

Leroi-Gourhan, A., 1958. Étude des restes humains fossiles provenant des grottes d'Arcy-sur-Cure (Yonne). Annales de Paléontologie 44, 87–148.

Leroi-Gourhan, A., 1961. Les fouilles d'Arcy-sur-Cure (Yonne). Gallia Préhistoire 4, 3–16.

Leroi-Gourhan, A., 1964. Le Geste et la Parole. Albin Michel, Paris.

Leroi-Gourhan, A., 1975. The flowers found with Shanidar IV, a neanderthal burial in Iraq. Science 190, 562–564.

Lévêque, F., Vandermeersch, B., 1980. Les découvertes de restes humains dans un niveau castelperronien à Saint-Césaire (Charente-Maritime). Comptes rendus de l'Académie des Sciences de Paris 291D, 187–189.

Li, J.Z., Absher, D.M., Tang, H., et al., 2008. Worldwide human relationships inferred from genome-wide patterns of variation. Science 319 (5866), 1100–1104.

Lordkipanidze, D., Jashashvili, T., Vekua, A., et al., 2007. Postcranial evidence from early Homo from Dmanisi, Georgia. Nature 449 (7160), 305–310.

Lordkipanidze, D., Vekua, A., Ferring, R., et al., 2006. A fourth hominin skull from Dmanisi, Georgia. The Anatomical Record. Part A Discoveries in Molecular, Cellular, and Evolutionary Biology 288, 1146–1157.

Lordkipanidze, D., Vekua, A., Ferring, R., et al., 2005. The earliest toothless hominin skull. Nature 434, 717–718.

McBrearty, S., Brooks, A.S., 2000. The revolution that wasn't: a new interpretation of the origin of modern human behavior. Journal of Human Evolution 39, 453–563.

McBrearty, S., Tryon, C., 2006. From Acheulean to middle stone age in the Kapthurin formation, Kenya. In: Hoverm, E., Kuhn, S.L. (Eds.), Transitions Before the Transition. Springer, New York, pp. 257–277.

McDermott, F., Stringer, C., Grün, R., et al., 1996. New Late-Pleistocene uranium-thorium and ESR dates for the Singa hominid (Sudan). Journal of Human Evolution 31 (6), 507–516.

McPherron, S.P., Alemseged, Z., Marean, C.W., et al., 2010. Evidence for stone-tool-assisted consumption of animal tissues before 3.39 million years ago at Dikika, Ethiopia. Nature 466 (7308), 857–860.

Mellars, P., 1996. The Neanderthal Legacy. Princeton University Press, Princeton, NJ.

Mellars, P., 2005. The impossible coincidence. A single-species model for the origins of modern human behavior in Europe. Evolutionary Anthropology 14, 12–27.

Mellars, P., 2006a. Archeology and the dispersal of modern humans in Europe: deconstructing the "Aurignacian". Evolutionary Anthropology: Issues, News, and Reviews 15 (5), 167–182. http://dx.doi.org/10.1002/evan.20103.

Mellars, P., 2006b. Why did modern human populations disperse from Africa ca. 60,000 years ago? A new model. Proceedings of the National Academy of Sciences of the United States of America 103 (25), 9381–9386.

Mellars, P., Gori, K.C., Carr, M., et al., 2013. Genetic and archaeological perspectives on the initial modern human colonization of southern Asia. Proceedings of the National Academy of Sciences of the United States of America 110 (26), 10699–10704.

Mercader, J., Barton, H., Gillespie, J., et al., 2007. 4300-Year-old chimpanzee sites and the origins of percussive stone technology. Proceedings of the National Academy of Sciences of the United States of America 104 (9), 3043–3048.

Mercader, J., Panger, M., Boesch, C., 2002. Excavation of a chimpanzee stone tool site in the African Rainforest. Science 296, 1452–1455.

Mercier, N., Valladas, H., Joron, J.L., et al., 1991. Thermoluminescence dating of the late Neanderthal remains from Saint-Césaire. Nature 351, 737–739.

Mishra, S., Gaillard, C., Hertler, C., et al., 2010. India and Java: contrasting records, intimate connections. Quaternary International 223–224 (0), 265–270. http://dx.doi.org/10.1016/j.quaint.2009.11.040.

Morgan, L.E., Renne, P.R., 2008. Diachronous dawn of Africa's middle stone age: new $^{40}Ar/^{39}Ar$ ages from the Ethiopian Rift. Geology 36 (12), 967–970.

Mortillet, G., 1897. Formation de la Nation Française. Plon-Nourrit, Paris.

Morwood, M.J., O'Sullivan, P.B., Aziz, A., et al., 1998. Fission-track ages of stone tools and fossils on the east Indonesian island of Flores. Nature 392, 173–176.

Movius, H.L., 1948. The Lower Paleolithic cultures of southern and eastern Asia. Transactions of the American Philosophical Society 38, 330–420.

Movius, H.L., 1953. The mousterian cave of Teshik-Tash, Southeastern Uzbekistan, central Asia. Bulletin of the American School of Prehistoric Research 17, 11–71.

Mturi, A.A., 1987. The archaeological sites of Lake Natron. Lac Natron, Sciences Geologique 40, 209–215.

Mulcahy, N.J., Call, J., 2006. Apes save tools for future use. Science 312 (5776), 1038–1040.

Napier, J.R., 1962. Fossil hand bones from Olduvai gorge. Nature 196, 409–411.

Nejman, L., 2008. A reinterpretation of early upper palaeolithic assemblages from Stránská Skála: the differences in lithic Economy between the Aurignacian and the Bohunician assemblages. Přehled Výzkumů 49, 24–45.

Noble, W., Davidson, I., 1996. Human Evolution, Language and Mind. Cambridge University Press, Cambridge.

Noll, M.P., Petraglia, M.D., 2003. Acheulean bifaces and early human behavioral patterns in East Africa and south India. In: Soressi, M., Dibble, H.L. (Eds.), Multiple Approaches to the Study of Bifacial Technologies. University of Pennsylvania Museum of Archaeology and Anthropology, Philadelphia, pp. 31–53.

Otte, M., 2003. The Pittfalls of using bifaces as cultural markers. In: Soressi, M., Dibble, H.L. (Eds.), Multiple Approaches to the Study of Bifacial Technologies. University of Pennsylvania Museum of Archaeology and Anthropology, Philadelphia, pp. 183–192.

Otte, M., 2010. Before Levallois. Quaternary International 223–224, 273–280.

Panger, M.A., Brooks, A.S., Richmond, B.G., et al., 2002. Older than the Oldowan? Rethinking the emergence of hominin tool use. Evolutionary Anthropology 11, 235–245.

Peresani, M., Cremaschi, M., Ferraro, F., et al., 2008. Age of the final middle palaeolithic and Uluzzian levels at Fumane cave, northern Italy, using ^{14}C, ESR, $^{234}U/^{230}Th$ and thermoluminescence methods. Journal of Archaeological Science 35 (11), 2986–2996.

Pickering, T.R., White, T.D., Toth, N., 2000. Cutmarks on a Plio-Pleistocene hominid from Sterkfontein, South Africa. American Journal of Physical Anthropology 111, 570–584.

Plummer, T., 2004. Flaked stones and old bones: biological and cultural evolution at the dawn of technology. Yearbook of Physical Anthropology 47, 118–164.

Porraz, G., Parkington, J.E., Rigaud, J.-P., et al., 2013a. The MSA sequence of Diepkloof and the history of southern African Late Pleistocene populations. Journal of Archaeological Science 40 (9), 3542–3552.

Porraz, G., Texier, P.-J., Archer, W., et al., 2013b. Technological successions in the middle stone age sequence of Diepkloof rock shelter, western Cape, South Africa. Journal of Archaeological Science 40 (9), 3376–3400.

Protsch, R., de Villiers, H., 1974. Bushman rock shelter, Origstad, eastern Transvaal, South Africa. Journal of Human Evolution 3 (5), 387–396.

Rayner, R.J., Moon, B.P., Masters, J.C., 1993. The Makapansgat australopithecine environments. Journal of Human Evolution 24, 219–231.

Riel-Salvatore, J., Clark, G.A., 2001. Grave markers. Middle and early upper Paleolithic burials and the use of chronotypology in contemporary Paleolithic research. Current Anthropology 42, 449–479.

Rightmire, G.P., 1984. *Homo sapiens* in sub-Sarahan Africa. In: Smith, F., Spencer, F. (Eds.), The Origins of Modern Humans. Alan R. Liss, New York, pp. 295–325.

Robinson, J.T., 1962. The origin and adaptive radiation of the Australopithecines. In: Kurth, G. (Ed.), Evolution und Hominization. Stuttgarter Verlagskontor Gmbh, Stuttgart, pp. 150–175.

Robinson, J.T., Manson, R.J., 1957. Occurrence of stone artefacts with *Australopithecus* at Sterkfontein. Nature 180, 521–524.

Roche, H., Delagnes, A., Brugal, J.-P., et al., 1999. Early hominid stone tool production and technical skill 2.34 Myr ago in West Turkana, Kenya. Nature 399, 57–60.

Rolland, N., 2004. Was the emergence of home bases and domestic fire a punctuated event? A review of the middle pleistocene record in Eurasia. Asian Perspectives 43, 248–280.

Ron, H., Levi, S., 2001. When did hominids first leave Africa? New high-resolution magnetostratigraphy from the Erk-el-Ahmar Formation, Israel. Geology 29, 887–890.

Ronen, A., 2006. The oldest human groups in the Levant. Comptes Rendus Palevol 5, 345–351.

Sabater Pi, J., 1984. El chimpancé y los orígenes de la cultura. Anthropos, Barcelona.

Schick, K.D., Toth, N., 1993. Making Silent Stones Speak. Simon & Schuster, New York.

Schlanger, N., 1994. *Châine opératoire* for an archaeology of the mind. In: Renfrew, C., Zubrow, E.B.W. (Eds.), The Ancient Mind. Elements of Cognitive Archaeology. Cambridge University Press, Cambridge, pp. 143–151.

Schlebusch, C.M., Skoglund, P., Sjödin, P., et al., 2012. Genomic variation in seven Khoe-San groups reveals adaptation and complex african history. Science 338, 374–379.

Semaw, S., Renne, P., Harris, J.W.K., et al., 1997. 2.5-million-year-old stone tools from Gona, Ethiopia. Nature 385, 333–336.

Semaw, S., Rogers, M., Stout, D., 2009. The Oldowan-Acheulian transition: is there a "developed Oldowan" artifact tradition? In: Camps, M., Chauhan, P. (Eds.), Sourcebook of Paleolithic Transitions. Springer, New York, pp. 173–193.

Simanjuntak, T., Sémah, F., Gaillard, C., 2010. The palaeolithic in Indonesia: nature and chronology. Quaternary International 223–224, 418–421.

Singer, R., Wymer, J., 1982. The Middle Stone Age of Klasies River Mouth in South Africa. University of Chicago Press, Chicago.

Solecki, R., 1975. Shanidar IV, a neanderthal flower burial in northern Iraq. Science 190, 880–881.

Steele, J., 1999. Stone legacy of skilled hands. Nature 399, 24–25.

Stringer, C., Gamble, C., 1993. In: Search of the Neanderthals (Ed. castellana, En busca de los neandertales. Barcelona, Crítica, 1996 ed.). Thames and Hudson, London.

Stringer, C.B., Trinkaus, E., 1981. The Shanidar neanderthal crania. In: Stringer, C.B. (Ed.), Aspects of Human Evolution. Taylor & Francis, London, pp. 129–165.

Szmidt, C.C., Normand, C., Burr, G.S., et al., 2010. AMS ^{14}C dating the Protoaurignacian/Early Aurignacian of Isturitz, France. Implications for Neanderthal-modern human interaction and the timing of technical and cultural innovations in Europe. Journal of Archaeological Science 37 (4), 758–768.

Taieb, M., 1974. Évolution Quaternaire du Bassin de l'Awash (Ph.D. dissertation). University of Paris VI.

Tchernov, E., 1987. The age of the Ubeidiya formation. Israel Journal of Earth Sciences 36, 3–36.

Tchernov, E., 1999. The earliest hominids in the southern Levant. In: Proceedings of the International Conference of Human Palaeontology, Orce, Spain, 1995. Museo de Prehistoria y Paleontologia, Orce, pp. 369–406.

Tchernov, E. (Ed.), 1986. Les Mammifères du Pléistocene Inférieur de la Vallée du Jourdain a Oubeidiyeh, vol. 5. Association Paléorient, Paris.

Tiercelin, J.-J., Schuster, M., Roche, H., et al., 2010. New considerations on the stratigraphy and environmental context of the oldest (2.34 Ma) Lokalalei archaeological site complex of the Nachukui Formation, West Turkana, northern Kenya Rift. Journal of African Earth Sciences 58 (2), 157–184.

Tobias, P.V., 1966. Fossil hominid remains from Ubeidiya, Israel. Nature 211, 130–133.

Toth, N., 1985a. Archaeological evidence for preferential right-handedness in the lower and middle Pleistocene, and its possible implication. Journal of Human Evolution 14, 607–614.

Toth, N., 1985b. The Oldowan Reassessed: a close look at early stone artifact. Journal of Archaeological Science 12, 101–120.

Trinkaus, E., 1983. The Shanidar Neandertals. Academic Press, New York.

Trinkaus, E., Shipman, P., 1993. The Neandertals. Changing the Image of Mankind. Alfred A. Knopf, New York.

Tryon, C., 2006. Le concept Levallois en Afrique. Fontation Fyssen – Annales 20, 132–145.

Vekua, A., Lordkipanidze, D., Rightmire, G.P., et al., 2002. A new skull of early Homo from Dmanisi, Georgia. Science 297 (5578), 85–89.

Vigilant, L., Stoneking, M., Harpending, H., et al., 1991. African populations and the evolution of human mitochondrial DNA. Science 253, 1503–1507.

Vogel, G., 1999. Chimps in the wild show stirrings of culture. Science 284, 2070–2073.

Vogel, J.C., Waterbolk, H.T., 1967. Groningen Radio Carbon dates VII. Radio Carbon 9, 145.

von Petzinger, G., Nowell, A., 2014. A place in time: situating Chauvet within the long chronology of symbolic behavioral development. Journal of Human Evolution 74, 37–54.

Wadley, L., 2010. Compound-adhesive manufacture as a behavioral proxy for complex cognition in the middle stone age. Current Anthropology 51 (S1), S111–S119.

Wanpo, H., Ciochon, R., Yumin, G., et al., 1995. Early *Homo* and associated artefacts from Asia. Nature 378, 275–278.

Washburn, S.L., 1957. Australopithecines; the hunters or the hunted? American Anthropologist 59, 612–614.

White, R., 2001. Personal ornaments from the Grotte du Renne at Arcy-sur-Cure. Athena Review 2 (4), 41–46.

White, T.D., Asfaw, B., DeGusta, D., et al., 2003. Pleistocene *Homo sapiens* from middle Awash, Ethiopia. Nature 423 (6941), 742–747.

Whiten, A., Goodall, J., McGrew, W.C., et al., 1999. Cultures in chimpanzees. Nature 399, 682–685.

Whiten, A., Horner, V., de Waal, F.B.M., 2005. Conformity to cultural norms of tool use in chimpanzees. Nature 437 (7059), 737–740.

Wilkins, J., 2013. Technological Change in the Early Middle Pleistocene: The Onset of the Middle Stone Age at Kathu Pan 1, Northern Cape, South Africa (Ph.D.). University of Toronto.

Will, M., Bader, G.D., Conard, N., 2014. Characterizing the late pleistocene MSA lithic technology of Sibudu, KwaZulu-Natal, South Africa. PLoS One 9 (5), e98359.

WoldeGabriel, G., White, T.D., Suwa, G., et al., 1994. Ecological and temporal placement of early Pliocene hominids at Aramis, Ethiopia. Nature 371, 330–333.

Wood, B., 1997. The oldest whodunnit in the world. Nature 385, 292–293.

Yamei, H., Potts, R., Baoyin, Y., et al., 2000. Mid-Pleistocene Acheulan-like stone technology of the Bose basin, south China. Science 287, 1622–1626.

Yellen, J.E., Brooks, A.S., Cornelissen, E., et al., 1995. A middle stone age worked bone industry from Katanda, upper Semliki Valley, Zaire. Science 268, 553–556.

Yuan, Z.X., Lin, Y.P., Zhou, G.X., et al., 1984. Field report of an excavation at Yuanmou Man's site. In: Zhou, G.X., Zhang, X.Y. (Eds.), Yuanmou Man. Yunnan People's Press, Kunming, China, pp. 12–22.

Zhang, P., Huang, W., Wang, W., 2010. Acheulean handaxes from Fengshudao, Bose sites of south China. Quaternary International 223–224, 440–443.

Zhu, R.X., Potts, R., Pan, Y.X., et al., 2008. Early evidence of the genus *Homo* in East Asia. Journal of Human Evolution 55 (6), 1075–1085.

Zhu, R.X., Potts, R., Xie, F., et al., 2004. New evidence on the earliest human presence at high northern latitudes in northeast Asia. Nature 431 (7008), 559–562.

Zilhão, J., 2006. Aurignacian, behavior, modern: issues of definition in the emergence of the European Upper Paleolithic. In: Bar-Yosef, O., Zilhão, J. (Eds.), Towards a Definition of the Aurignacian. American School of Prehistoric Research/Instituto Português de Arqueologia, Lisboa, pp. 53–69.

Zilhão, J., d'Errico, F., Bordes, J.G., et al., 2006. Analysis of Aurignacian interstratification at the Chatelperronian-type site and implications for the behavioral modernity of Neandertals. Proceedings of the National Academy of Sciences of the United States of America 103 (33), 12643–12648.

Chapter 45

Biology, Psychology, Ethics, and Politics: An Innate Moral Sense?

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The underlying premise of social science is that certain human behaviors occur with enough regularity, across time and geographic and cultural space, that we can speak with confidence and a sense of predictability about the institutions and functioning of human society and the interpersonal relationships of individuals as members of that society. The goal of the social scientist is to determine what these behaviors are, the conditions under which they hold, and then develop theories of social life that incorporate these behaviors about our daily life into theories and models of human behavior. At the founding of social science, as the 19th century turned into the 20th, this premise was hotly debated, with many scholars arguing that cultural variations were so great that all behavior was contextual. Vilfredo Pareto supposedly landed in the middle of this debate when he gave a lecture at Lausanne and spoke of the science of economics. A questioner in the audience challenged Pareto, insisting there were no rules of economics, no consistent behavior, and hence economics was not a science in the same way that physics or biology would be a science.[1]

Pareto's answer was surprising: "Are there good restaurants in Lausanne?"

The audience thought Pareto had lost it, and the questioner responded, a bit disdainfully, "Of course!"

"So I can get a good meal here after the lecture?" Pareto continued.

"Of course," was again the scornful reply.

"Well, are there any restaurants where I can eat for free?" Pareto countered.

"No. That's ridiculous. You have to pay when you go to a restaurant."

"Ah, yes," was Pareto's response. "Congratulations! You have just discovered a law of economics."

This possibly apocryphal anecdote illustrates both the strength of the assumption that social science is indeed a science and the problem with the assumption: What behaviors occur frequently enough that we can speak of them as part of a human social science? Nowhere is this quandary greater than in the area of ethics and morality.

When asked where ethical behavior comes from, and what causes it, most laymen and—probably—most scholars immediately think of religion or socialization. We are taught what is right and wrong by our parents, by our faith, by studying great philosophical systems, such as Utilitarianism or Kantian ethics. Largely forgotten in contemporary analyses of morality and ethics, certainly among the dominant philosophical approach in the United States and Western Europe, is moral sense theory. In this chapter, I want to discuss moral sense theory and how it relates to the general theme of this volume, which concerns what we think of as human nature.[2]

I begin by asking: What is moral sense theory? Why is it important for ethics? What can a consideration of recent work in biology and psychology tell us about an innate moral sense? In addressing these questions, I cite convincing scientific evidence, in fields as wide ranging as child development, linguistics, behavioral economics, neuroscience, moral psychology, and primatology, that supports the belief in universal drives that can be said to constitute a biologically prepared moral architecture within human nature. Not limited to self-interest, these include what might be called a moral sense, akin to the olfactory lobes that provide us with a sense of smell. This evidence suggests all human beings are born with the prototypes of a sense that fosters anxiety when they witness others in distress and, similarly, promotes positive feelings when that distress is alleviated. Indeed, some empirical work suggests

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00045-4

that incorporating the concept of an innate moral sense into our basic models of social and political life will improve ethical analysis.

The analysis presents an overview of moral sense theory and its criticisms in Part 1. Part 2 turns to recent scientific evidence suggesting human beings are born with substrates of a moral faculty hardwired into their neural circuitry. The normative implication is that agents of socialization traditionally said to inculcate ethics actually may be reinforcing parts of an instinctive moral sense. Part 3 suggests what this evidence sheds on the basic tenets of moral sense theory. It then proposes critical questions that might inform research as we scrutinize this old theory via a more focused, scientifically informed, interdisciplinary examination.

Analysis emphasizes three points. (1) It challenges existing claims for strong cultural relativity.[3] Instead, the empirical evidence supports claims of an innate human nature that varies, according to the environment—broadly conceptualized—in phenotypic fashion. (2) Ethical theories and models based on psychological egoism leave unexplained much of political behavior since they rest on too narrow a conceptualization of human nature, and they omit crucial elements of the sociability that moral sense theory places as a fundamental part of our human nature. In this regard, my chapter relates closely to other chapters on altruism. Finally, (3) the conclusion calls for increased continuing dialogue with other disciplines since, as the present illustration demonstrates, interdisciplinary work with the natural sciences can yield important insight into basic tenets of ethics. The need for this kind of integrated interdisciplinary work illustrated the value and the intellectual significance of the current volume.

THE ORIGINAL MORAL SENSE THEORY

As a philosophical theory, moral sense theory holds that we are able to distinguish between right and wrong through a distinctive moral[4] sense.[5] Although human nature is a perennial philosophical theme, dating from Plato, the idea of an innate moral sense reflects the Enlightenment's attempt to explain how human psychology might justify political and moral theories.[6] As part of the Enlightenment's quest for the scientific analysis of moral issues, moral sense theory inquires about the realities of human nature to construct our disquisitions on government and moral conduct on this nature and, presumably, construct polities that then can more realistically hope to achieve an ethical politics and society. In this regard, we discern the influence of both Locke and Hobbes.

In *An Essay Concerning Human Understanding* (1690/2000), Locke attempted to develop a mental science much as Isaac Newton had developed a physical science. Locke was not the only scholar to reject the scholasticism and rationalism of his time, and to eschew the approach in which we deduce "truths" from abstract premises that were otherwise unavailable to ordinary experience. In this, Locke followed the scientific tradition of both Newton and Bacon in stressing an approach that attempted to discern the nature of human beings through an empirical method that was systematic and available to anyone who had ordinary powers of perception and unprejudiced judgment.[7]

This scientific approach to morality rejected the approach in which abstract rationality reduces the senses to a minor role. It generated a school known as moral sense theory, also referred to as British sentimentalism.[8] Moral sense theorists argued that moral terms must refer to something that is ultimately observable. The reference of such terms is a sentiment or a feeling of revulsion or approval. The moral quality of any act is the sentiment it elicits, and the core of morality is a distinctly human nature that is inclined toward social and political forms of connection. This makes the moral sense a substrate of all human behavior. At its core, it remains the same, despite cultural variations.

Hobbes's influence on moral sense theory is less direct than Locke's but nonetheless powerful. Perhaps we best discern Hobbes's influence by noting that moral sense theory attempts to answer both the questions left unanswered by theorists who find reason the driving force behind moral action, and the questions left unanswered by the intuitionists who opposed the primacy of reason. The problem for those who argue in favor of moral intuitions—as opposed to reason—as the impetus for morality is the following: If reason does indeed tell us it would be wrong to be immoral—to lie, for example—how does this discernment provide a *motive* to be moral? Is merely recognizing that something is wrong enough to move us to do the right thing, even when our desires suggest otherwise? For example, why would we not lie anyway, if lying is in our self-interest in a particular instance? The intuitionist position separates our moral knowledge from the forces that motivate us. Intuitionists make moral knowledge a matter of reason; but they locate our drive toward selfishness—such as lying or other forms of immorality—in the passions. This then raises obvious questions: Will reason dominate the passions? What happens if it does not?

An answer from religion is the blessing and sanction of God; the deity will react punitively in the absence of control of our selfish passions. Others (Durkheim) found an answer in the socializing role of community. Hobbes answered this same question via the strong sovereign of social contract theory. In all these explanations, we are compelled to act morally by an external force, whether sacred (God) or secular (society or the political authorities). The external thus provides the impetus to do good. These answers were unacceptable to the intuitionists, who wanted

to demonstrate that morality had innate bases within human beings themselves and that it is reasonable to do good *regardless* of threats from any external power, divine or human. It is the attempt to construct such a demonstration that lies behind moral sense theory. Although the initial discussion occurred during the 17th to 18th centuries, the debate touches on an issue still under contention today: does the drive toward morality lie in conscious reasoning or in affective processes?

Shaftesbury

The term "moral sense" was first used by Shaftesbury, who argued we are able to distinguish between right and wrong by a distinctive moral sense that provides a special type of affective response. For Shaftesbury, the ability to sense virtue was akin to an aesthetic act, comparable to sensing beauty in art. Both senses have much to do with whether an act contributes to the general harmony of mankind. Therefore, the moral sense as such is closely related to considerations of the general welfare.

Shaftesbury[9] argued against the Hobbesian view that the prime motivation driving human behavior is self-interest. For Shaftesbury, Hobbes erred in privileging self-interest as an explanation; Shaftesbury agreed that self-interest is a natural passion in humankind but held that self-interest is but one of many passions. Shaftesbury claimed that self-interest is joined (and often superseded) by other passions, such as benevolence, sympathy, gratitude, and generosity. For Shaftesbury, these feelings create an "affection for virtue," which then naturally leads to the promotion of public interest. This affection, which Shaftesbury thought created a natural harmony between virtue and self-interest, was called the moral sense. Shaftesbury thus recognized that people had contrary desires, of the kind made central by Hobbes, and did not expect people to be virtuous at all times. But he contended that the pleasures of virtue are superior to those of vice and expected that the dual motives of self-interest and the social interest would work together in perfect adjustment.

The originator of the theory thus set it up as a distinctive moral sense. It is a feeling–response, analogous to sensing beauty. For Shaftesbury, the test of a proposed action was whether it contributes to the general harmony of mankind, which Shaftesbury identified as the general welfare. This harmony of the senses follows the Greek tradition (eg, Plato) in which the harmony of the two drives in human nature—that of self-interest and social interest—work together in equilibrium. For moral sense theorists, as for other Enlightenment thinkers, morality does not require supernatural sanctions and religion. Nonetheless, while religion is not critical for moral sense theory, the early moral sense theorists were at least nominally Christian and did allow that it may be God who implanted this moral sense in man. Moral sense theory thus is not antithetical to religious views of a moral sense, and it might be said merely to substitute nature for God as the key agent, as the Deist responses of the Enlightenment made plain. But the spurs to moral activity have their base in human nature, extraneous to religious sanction and prior to deliberative reason.

Hutcheson

Shaftesbury's general ideas are expanded upon by Francis Hutcheson, whose analysis of human nature claimed there were a great number of special senses.[10] Essentially, Hutcheson argued that humans possess more than just the five external senses that allow us to smell, taste, see, hear, and touch. We also have a variety of internal senses. These internal senses include a sense of honor, of beauty, a sense of the ridiculous, and more important for our purposes, what Hutcheson called a "public sense" that entailed the feeling of being pleased by the happiness of others and uneasy over human misery.

According to Hutcheson, these internal senses are implanted in us, much as are the senses of taste, smell, etc. These internal senses cause us to react immediately and instinctively to the character of actions. The moral sense causes us to approve of acts that are good and virtuous and to disapprove of those that are bad or vicious, much as humans exhibit disgust at foul odors or salivate in the presence of food. Hutcheson went even farther than the original intuitionists in asserting that moral judgment is not based on reason. He held that our moral sense does not simply, or even predominantly, find pleasing those acts that benefit our own interest. For Hutcheson, moral sense seems based on a disinterested benevolence, with the ultimate desideratum "the greatest happiness for the greatest number." (This argument anticipates the Utilitarians in both phrasing and in its concern to promote the general welfare à la Bentham.)

Hutcheson suggested the moral sense is an internal reflex, responding both to external and internal precepts. While custom, education, and example may refine and even extend this sense, a natural substrate or proto-sense must exist to perceive the moral right and wrong. Hutcheson based part of his argument on the fact that benevolence is pleasing to man. He maintained that since man's power to reason is, in general, too weak to match his moral perceptiveness, there must be a moral sense to which benevolent activity is pleasing. This approach later appeared in work by Hume and Adam Smith,[11] Hutcheson's most famous student.[12]

Hume

David Hume agreed that reason cannot constitute the foundation for morality since reason, for Hume, is the slave

of the passions.[13] Reason cannot determine our ultimate desires and cannot move us toward action unless there is a prior desire; all it can do is tell us how best to achieve these desires. For Hume, all substantive knowledge ultimately must be derived from sense experience. But Hume broke with his predecessors who sought to provide a rational warrant for most of our original beliefs and held that many beliefs had no such warrant. Instead, Hume contended, they should be explained in psychological terms. They were the results of mental processes of a non-rational, though practically irresistible kind. Hume drew particular attention to the role played by the imagination, and the importance of the imagination as a source of conventional rules and custom.

Contemporary work in neuroscience and cognitive psychology confirm many of Hume's claims. Among philosophers, however, Hume's argument—that ethics is rooted in emotion or feelings instead of reason—moved the debate away from the specific claim of a moral sense, and Hume is conventionally understood to be arguing primarily for the predominance of emotion as the foundation of ethics rather than to be arguing in favor of a specific moral sense. In this regard, Hume's heirs are the students of human nature and the historical development of society, and we find the concept of a moral sense surfacing most prominently among developmental psychologists concerned with ethics[14] and ethologists concerned with the extent to which human beings resemble other animals in having an inborn sense of morality, much as they have an instinct for survival.[15]

Moral sense theory was strongly criticized,[16] and the main currents in Western philosophy have largely ignored ideas linking[17] morality with natural, affective faculties. For example, Marx and Engels[18] reduce morality to a kind of ideological reflex that is the epiphenomenal by-product of the concrete, material life and the relations of production. Certain varieties of analytic philosophy attempt to rigorously distinguish values from facts and question whether moral statements have any validity at all.[19] Certainly, Kant helped make deliberative reason the privileged site of moral judgment. Contemporary Anglo-American ethics[20] generally argues that reason provides the foundation for moral duty, helps us discover what morality is, and constitutes the tool by which we reach agreement when we disagree over or are torn by the particulars of moral choice.

CONTEMPORARY EVIDENCE OF A MORAL SENSE

Despite this lack of attention to the idea of an inborn moral sense among philosophers and political scientists, the idea nonetheless perseveres in other disciplines. Arguments that human beings have an inborn sense of morality, much as they have an instinct for survival, surfaces prominently in the contemporary literature of a wide variety of quite diverse disciplines. Ethology and anthropology, for example, share a concern for human sociability and ask whether there are behaviors, such as mothering, that are socially constructed or if such behaviors contain an innate element. Anthropologists ask about human behavior in the ancestral environment to discern the role of culture in influencing moral behavior. Animal ethologists ask if the ethical nature of human beings is rooted in the biological nature we share with other species. Developmental psychologists examine children in their earliest years, before culture and language have shaped what might be innate tendencies toward certain kinds of behavior. And, increasingly, moral psychologists and neuroscientists are making inroads into the biological substrates of moral behavior not only in animals or infants but also in adults throughout the life cycle.

Some of the empirical research described next can be fragmentary and preclusive; it occasionally involves questions about the scientific reliability of certain findings.[21] Nonetheless, this evidence is salient enough to justify a reconsideration of the existence of an innate moral sense. We need to ask if this assumption, or at least its possibility, should be built into our political models.[22]

Developmental Psychology

Contemporary psychologists build on Piaget[23] who, while not explicitly proposing a moral sense, did assume people have a built-in capacity for morality. Piaget's heirs[24] privilege reason in constructing cognitive-developmental models that tie the idea of an innate moral sense to developmental reasoning as they ask how people progress through different stages of moral reasoning and, later, ask how factors such as gender influence a general developmental process that exists innately in all humans. Analysts such as Kohlberg[25] and Gilligan,[26] however, made moral development an extended process, wherein moral reasoning continues to develop well into adolescence and adulthood. Because their work emphasized reason, not an innate moral sense, it thus has only a tangential relevance for us.[27] Other child psychologists (Kagan, Lamb) provide clearer illustrations of developmental work arguing for an innate moral sense, work that does not rely on more complex cognitive processes of reasoning of the kind found only in adolescents or adults.[28] Let us thus turn to work on child development, treating research by Jerome Kagan, one of the most important developmentalists, as illustrative of the genre.

Kagan's lifetime of experiments with children asks whether human action is motivated by a desire for sensory pleasure. He finds the emergence of a moral sense in children at the end of the second year is universal and, perhaps more than language or reason, distinct to people.

Humans seem biologically programmed with an innate moral sense of ethics and morality, much as we are programmed for language. As with language, the form this ethics takes in practice will vary according to external factors. In making this argument, Kagan juxtaposes what he considers an innate moral sense in children with the kind of explanation offered by Utilitarians, who root the drive for ethics in the desire to maximize pleasure and minimize pain. Kagan concludes that the conscious feeling of pleasure that originates in one or more of the sensory modalities—those found in the sensory pleasure at eating food, touching something that appeals to us, or in sexual arousal—are indeed innate. But it is not this kind of pleasure that Kagan makes critical in his conceptualization of a moral sense. Instead, Kagan (1998, p. 151) locates a moral sense in the "conceptual consonance between an idea, called a standard, and the chosen action. When that consonance occurs, the person momentarily experiences a pleasant feeling because his behavior is in accord with a standard he has categorized as good."[29]

This distinction is critical for our purposes. Kagan claims the pleasures of sensory experience discussed in Utilitarian thought can be confirmed with laboratory investigations. This particular sensory pleasure is found in a variety of animals, not just in humans. In the mammalian brain, this sensory pleasure centers in a set of neurons that, when excited, create a state of sensory enjoyment. Biological tests confirm the existence of such neuronal transmitters and reveal activity in the centers of the brain in which such sensory stimuli originate. For theorists who locate the drive toward morality in such a sensory pleasure, then, scientific evidence seems to validate the existence of such pleasure centers.[30] Nonetheless, Kagan notes, attempting to root morality in sensory pleasure still involves us in difficulties. "The traditional argument that moral standards are derived from sensory pleasure or the reduction of pain cannot explain the universal fact that people become angry when they see others violate standards they believe are right" (1998, p. 158). Does this mean we must abandon the idea of a moral sense? Not for Kagan, who argues that the biological foundation of this moral sense is critical, and emerges from our primate ancestry. But the good feelings, the pleasures that come when we experience consonance with our standards, *these* are what Kagan argues drive us toward moral action, and these are as difficult to measure as they are critical for morality. Kagan proposes that these more complicated good feelings consist of five unique abilities that humans inherit genetically, much as both humans and other primates inherit the tendency to be attentive to the voice, face, and actions of others. For Kagan, these five components constitute the moral sense: (1) the ability to infer others' feelings and thoughts,[31] (2) the capacity for self-awareness, (3) our penchant to categorize events and ourselves as good or bad, (4) our capacity to reflect on past actions, and (5) our capability to know that a particular act could have been suppressed. These five abilities exist in all human beings. They merge to form a moral sense around the second year in children, thus making the human moral sense a biologically prepared competence.

These developmental arguments about our moral sense correspond to arguments about our innate mathematical abilities. The human ability to conceptualize numbers and grasp the rules of arithmetic is innate,[32] but an innate mathematical ability does not necessitate the particular set of mathematical principles that has been conceptualized and passed on to us as children. The form of the mathematics is arbitrary; other principles could equally well have been generated and transmitted. Thus, although a foundation for a moral sense *does* exist, the mere existence does not necessarily imply that a *particular* ethical system is more natural than others. The wide "variety of moral standards across cultures in history" supports Kagan's (1998 p. 12) claim that it is "very difficult to argue that one inherits a tendency for certain morals." In this regard, ethics resembles language.

> *[B]ecause we're humans, we inherit a capacity to learn a language. But the language that we learn could be Swahili, French, English, Japanese. The same thing [is true] with morality. We inherit, because we are humans, a concern with right and wrong, and empathy with others. But the specific actions that we regard as moral, can vary with culture, just as the specific language you learn can vary with culture.*
>
> Kagan (1998, p. 13)

The proclivity toward ethical behavior thus is innate, but the particularities of the ethical action are not. Accordingly, a cultural relativist could accept the concept of an innate moral sense while still arguing that what some ethicists find an innate prohibition—a taboo against incest or murder, for example—is socially constructed. Despite this conclusion, Kagan argues against cultural relativism when discussing the stages reached by normal children.[33] These stages include the cognitive sophistication necessary to integrate the past, present, and future in what Piaget called reversibility, a process necessary for the assumption of responsibility for one's actions.[34] Most 2-year olds have a capacity to "infer the thoughts and feelings of another and will show signs of tension if another person is hurt, or may offer penance if they caused another's distress" (Kagan, 1998, p. 173). The ability to anticipate the feelings of another is linked with the suppression of the child's desire to hurt that person. This connection between empathy and anticipation of another's feelings, however, is the result of speculation and inference, not the result of experiments. Nonetheless, the "appearance of empathy in all children by the end of the second year implies that two-year-olds are

prepared by their biology to regard hurting others as bad—that is, [as] a moral violation" (Kagan, 1998, p. 173). At the same age, most children become aware of themselves as individuals with specific characteristics, intentions, and feelings. They recognize that they can be labeled "bad" or "good" and will try to avoid creating unpleasant feelings in others since they know that if they do so, they in turn will be avoided (Kagan, 1998, p. 173).

> *That insight is a seminal origin of the moral motive, although it will not be the only basis for morality in later years. A desire to avoid or to deny the labeling of self as bad increases in intensity as the child matures; in time, it will take precedence over fear of disapproval or punishment as the primary governor of behavior. This means shame and guilt are biologically prepared, developmentally timed emotions.*
>
> (Kagan, 1998, p. 175)

Child developmentalists—such as Kagan—do not take us to specific morality, just to our need to classify acts as "good" or "bad." We find little in his system to distinguish an Oskar Schindler from a Nazi genocidalist. Nor do they totally separate morality from a developmental process that controls out the influence of reason and culture, although references to cross-cultural studies allow for many cultural factors. For this, we turn to literature in primatology that attempts to achieve both these goals, and which suggests animals *other than* human beings have a moral sense that is expressed in specific behaviors. Such works are not referring to the kind of consonance between act and standard that Kagan makes his hallmark of morality. Further, Kagan himself would take strong exception to classifying other animals in the same category as humans, since Kagan holds humans the only species to have the particular form of a moral sense that moves beyond the pleasure principle or psychological egoism.[35] This view from one of the key child developmentalists, then, is that the human moral sense is biologically prepared, that it develops early, and that it is adaptive, a product of evolution unique to human beings. "That's why a lot of the animal research that tries to inform the human condition has limited value because we, only we, not chimpanzees, are aware of right and wrong, and we wish to do the right thing" (Kagan, 1998, p. 11).

Evolutionary Biology and Animal Behavioral Economics

Other scholars take strong exception to Kagan's insistence on the unique human claim to a moral sense. In searching for biology's ability to encode behavior, they focus on primitive behaviors that do not require the cognitive development Kagan required for his moral sense as consonance (For example, Darwin[36] embraced the concept of a moral sense but did not specify what he meant by it.). Do animals exhibit behavior that corresponds with what we humans think of as "moral"? Do nonhuman animals feel the kind of sentiments that Hume made the impetus for morality? Do animal possess the cognitive abilities necessary to engage in the relatively sophisticated developmental processes underlying Kagan's concept of morality as consonance? If so, which animals? Where do we draw the line in terms of cognitive development? Is animal behavior that looks moral to us the product of more primitive stimulus-response patterns that occur without the complex neurotransmitter responses of the neo-cortex? A host of questions remain to be answered, but the preliminary evidence is intriguing.

Relatively few works by evolutionary biologists focus on morality among human beings. Consequently, this literature does not often find its way into discussions of human morality, and evolutionary biological analyses of a human moral sense seldom are found in contemporary political science.[37] For empirical, albeit still controversial, evidence on the idea of a moral sense, we turn to scholars studying animal behavior, especially primatology. These animal behavioral scientists do not adopt Kagan's conceptualization of a more cognitively developed consonance; yet Kagan and animal ethologists share one important theme: disputing the idea that the only drive behind behavior is psychological egoism. Their success in this endeavor has salience for political science, since psychological egoism is the sole or dominant force for many political theorists (Hobbes) and evolutionary biologists[38] who argue that human beings resemble other animals in being born selfish and lacking in true generosity and altruism. Animal behavioral scientists[39] challenge this view, and they offer intriguing evidence to support their view that animals have an innate moral sense.

Much of this literature is designed to demonstrate that morality is not merely man's cultural invention but is instead the product of millions of years of evolution. These evolutionary biologists concede that the strong have an advantage in any society built on individual strength. But this advantage shifts once additional factors relevant for survival are introduced. Any complex society, they argue, will make cooperation a valued form of behavior and thus evolutionarily adaptive. Working together helps individuals—be they capuchin monkeys or human beings—who do better than they would alone. In game theoretic terms, joint efforts produce joint payoffs; with cooperation comes increased sensitivity concerning who gets what for their efforts. Thus, some evolutionary biologists find the Hobbesian world mischaracterizes empirical reality. Instead, animal behavioral economics turns to the Adam Smith of *A Theory of Moral Sentiment*s, emphasizing the way in which kindness begets kindness. They argue that human beings have a concern with fairness and justice, but some[40] critique political theorists[41] for focusing on how much we care about

fairness when we should be asking *why* primates came to care about justice and fairness in the first place. Animal behavioral economists argue that humans come from a long line of social primates and believe there are quite concrete advantages associated with fairness in our primate past.

These conclusions are supported by a host of empirical studies, from animals as diverse as chimpanzees and lions to fish and humans.[42] Chimpanzees will groom in exchange for food, for example, suggesting memory-based and partner-specific exchanges that mimic what humans call gratitude.[43] Research on capuchins suggests they demonstrate cooperation, communication, and even obligations, as when two monkeys work together to get the reward of individual bowls of food.[44] Monkeys demonstrate a sense of fairness, protesting when one monkey gets grapes (a preferred food) while the others get cucumbers, even going on strike until they all get grapes.[45] The monkeys thus seem to reject unequal pay, behavior at variance with the fitness maximization, which stipulates they should take what they can get and not let another's resentment or envy interfere with maximizing behavior.

Behavioral economists argue that the evolution of emotions serves to preserve the spirit of cooperation. Caring what others get might seem irrational to some schools of economics, but it keeps us from being taken advantage of in the long run.[46] Discouragement of exploitation, free-riding, and cheating thus is evolutionarily advantageous. Such empirical work has been developed into a sophisticated theory of cooperation, mutual aid, gratitude, reciprocity, and sharing.[47] Mammalian preferences for equity have been found among dogs, not just among primates.[48] These experiments in animal behavior conclude that the source of the fairness principle is conflict avoidance. It begins with individual animals noticing resentment and their concern about how others will react if one animal gets more. It ends with more complex declarations proclaiming inequity a bad practice in general. Human beings thus "embrace the golden rule not accidentally, as Hobbes thought, but as part of our background as cooperative primates" (DeWaal in Markey, 2003). In this sense, animal behavioral scientists might provide one answer to an important criticism posed to the original moral sense theorists: How do we choose between the various—and conflicting—behaviors that people judge moral? One plausible answer is to favor whatever behavior is more evolutionarily adaptive.

But what if we reject this route as too simplistic? Is the literature on animal behavior still relevant for us? Yes. If we are asking about an innate moral sense, and whether or not human beings possess this sense, then an important way to approach the problem is to conceive of humans as a subset of the animal kingdom. If other animals, especially primates—of which humans are a subset—demonstrate behavior that appears to correspond to what we would conceptualize as moral, then that constitutes inferential evidence suggesting human beings possess this moral sense as part of our animal biology.

Humans and Their Primate Nature

Drawing on more than 25 years of experiments with primates, primatologists such as Frans DeWaal argue that an innate moral sense exists in all primates, and that animals have both culture and emotions.[49] This work challenges both the philosophical tendency to privilege human beings and the premise that self-interest drives our animal nature.[50] "[M]orality is as firmly grounded in neurobiology as anything else we do or are" (DeWaal, 1986, p. 217). Indeed, DeWaal finds a wide range of ethical acts among primates, from reciprocity and cooperation to helping those who are hurt or feeding the hungry. Such acts, for DeWaal, indicate the ability of animals to feel sympathy. "Survival of the weak, the handicapped, the mentally retarded, and others who posed a burden was depicted as the first appearance on the evolutionary scene of compassion and moral decency" (1996, p. 7). He cites numerous examples of animal succorance demonstrating the "functional equivalent of human sympathy" in animals as different as whales and macaques (1996, p. 40). DeWaal further argues that animals respond to social rules to help each other and to share food and resolve conflicts. He does not argue that animals are morally good, but he does claim they exhibit behavior that looks like cooperation, altruism, sharing, helping, etc., *in addition to* demonstrating the kinds of behavior that ensures survival. His picture of animals, then, is a more complex picture of morality than that usually attributed to animals in a simplified model of Darwinian "survival of the fittest." Whether this behavior in animals corresponds to what we think of as moral, and whether we should further infer from this behavior that there is an underlying animal emotion that corresponds to the human emotions that drive similar behavior on our part are two important questions DeWaal does not address directly.

DeWaal does provide extensive evidence from animal behavior, however, that suggests animals exhibit behavior suggestive of an inborn sense that corresponds closely to what we might think of as morality. He provides numerous illustrations suggesting all social mammals—from elephants and dolphins to primates as well as humans—share four distinct characteristics that constitute the roots of a moral system. These traits are sympathy, hierarchy, reciprocity, and reconciliation.

Sympathy

DeWaal's observations of primates suggest all social mammals recognize each other as individuals and have feelings for each other. These feelings include sadness at long separations, happiness on being reunited, and the drive to help members

who are in trouble in their community. Demonstrations of sympathy and concern include dolphins supporting an injured companion at the water's surface to keep it from drowning, an elephant returning to the spot where his mother died and touching her skull sympathetically, or an elephant herd trying to revive a young female elephant who was shot by a poacher and then, when their helpful efforts provided unsuccessful, spreading earth and branches over her body before they leave it. DeWaal argues that sympathy is the cornerstone of morality. It is sympathy that leads us to recognize the existence of others and to treat others with the consideration we would like to have shown us.

Hierarchy

DeWaal next suggests animals exhibit an inborn drive for hierarchy, another characteristic of morality he finds shared by animals and humans. Generally, DeWaal notes, all social mammals live in hierarchies and follow the rules enforced by the dominant group. Once the social order is established, breaking this order leads to the anticipation of punishment.[51] Primates will administer beatings, among other forms of punishment, to group members who break group rules.[52] DeWaal finds such behavior resembles the human need to enforce the rank and order of a community through the institutions of law, politics, and government. For DeWaal, this demonstrates a sense of culture and a society that has rules and regulations that must be abided by. For the animals DeWaal studied, when behavior deviated from the norms of the group, punishment was effective, and the established order was maintained.

Reciprocity

DeWaal notes a phenomenon closely related to dominance and hierarchy: reciprocity, a kind of quid pro quo that exists in all primate communities. Male chimpanzees, for example, pursue dominance and form coalitions that depend on mutual support during confrontations with their rivals. Repeated failure to support a partner destroys the coalition. Moreover, DeWaal find some primates appear to remember who has hit them and will take revenge on these individuals afterwards. Even in sharing food, primates tend to share food with those who have shared food with them in the past. For DeWaal, this parallels the human need for fulfillment of obligations and keeping agreements. DeWaal concludes that primates have the intuitive ability to be generous and to expect a similar show of generosity in return.

Reconciliation

Finally, primates appear to resolve communal conflict over food, resources, and other social incidents in a similar manner. Reconciliation has to occur, and third parties play an important role in eliminating the conflict. Primates do this through grooming, embracing, or kissing in patterns that DeWaal finds evocative of forgiveness and mediation to maintain the peacefulness in the human community.

Space constraints limit fuller discussion of this research, but DeWaal's work illustrates the trends among primatologists to view human beings in evolutionary terms, not as a distinct moral species.[53] What we find in human beings, they argue, is a difference in degree, not a difference in kind. Thus, nonhuman animals share distinct aspects of a moral system that are akin to that of their human cousins. In particular, primatologists have gathered clear and striking scientific evidence that suggests psychological egoism is *not* all there is to our inherent primate nature. If our social nature exists as part of our primate genotype, our political theories should recognize this. When broken down to its most essential indicators—culture, language, and politics—morality can be found in animals. If it exists in all primates, the conclusion then must be that it exists in man as well, as part of our primate nature.[54]

Behavioral economics also sheds light upon how the presence of basic "moral emotions" could lead to cooperative economic outcomes. Bowles and Gintis have modeled a public goods game whereby in addition to personal material payoffs, subjects' utility functions can incorporate one's valuation of the payoff to others, one's "degree of reciprocity," and moral emotions such as guilt of shame at one's own or another's deeds; these factors can promote cooperation in a group setting. This tendency, they propose, points to the role of internalized norms building upon the moral emotions to construct socially optimal results. Such an "internalization of norms" serves to "eliminate(s) many of the cost-benefit calculations and replaces them with simple moral and prudential guidelines for action" (Bowles and Gintis, 2002, p. 21). This means norm-internalizers are more "biologically fit than those who do not [internalize norms] so the psychological mechanisms of internalization are evolutionarily selected" (2002, p. 21).

The evolutionary and genetic implications of these findings have been plausibly modeled as well.[55] Such an approach provides a valuable addendum to the self-interest-based models[56] and its cognate parallels in biology.[57] In experimental situations, drives toward social motives—such as equality—have also been noted. Dawes et al. (2007) found that in constructing a game isolating egalitarian motives, participants would alter the incomes of other players even at a cost to themselves, given a chance, when inequality was perceived. In other words, players' negative affect at inequality drove them to "reduce above-average earners' incomes and to increase below-average earners' incomes" (2007, p. 794). Dawes and his colleagues believe such behavior points to the evolutionary development of "strong reciprocity."[58] This is an exciting area, and I expect much work in this field in the future.[59]

A Moral Grammar

Recent work builds on this analogy but substitutes Chomsky's[60] model of innate linguistic grammar for math[61] and links this to Rawls's (1971) work on justice.[62] This work draws on evolutionary psychology, biology, linguistics, neuroscience, and primate cognition to argue that humans are endowed with a moral faculty that pronounces on right and wrong based on principles of action that are unconsciously derived.[63] The moral grammar consists of a set of principles that operate on the basis of the causes and consequences of action. Hence, just as humans are endowed with innate capacity for language, we also possess a moral faculty. We are born with a sense of abstract rules or principles. Nurture enters the picture to set the parameters and guide us toward the acquisition of particular moral systems. Empirical research distinguishes the principles from the parameters to discover limitations on the range of possible moral systems. It may be that the brain acts as a circuit, like a toolkit specializing in recognizing certain problems as relevant for ethics. Many of the experiments here try to delimit stages in child development. For example, Hauser finds that 3-year olds are already aware of intention. They judge less severely acts that cause harm when the intention is good. Hauser deems this ability an innate way to detect cheaters who violate social norms.[64] Hauser rejects the Kantian perspective on morality as relying too exclusively on reason and principles, finding this Kantian view undermined by research[65] into the emotions.[66] This suggests people do not act by principled reasoning alone. Indeed, when questioned after an action, people frequently cite gut feelings or intuitions as their motivating force. Hauser also rejects the Humean position, however, which predicates the validity of a moral judgment on how one feels. If morality simply resides in how one feels—ie, it is grounded in individual self-reference—then, moral pronouncements would be infinitely heterogeneous, atomistic, and internally inconsistent with a concept of morality as a referential behavior for a collective.[67]

Different locations (attitudes toward a moral dilemma) can be explained as variation from some mean. This is where the innate grammar analogy comes into play.

> *Paralleling the story of language, one path to discovering whether our moral faculty consists of universal principles and parameters that allow for cultural variation is to tap into the anthropological literature with its rich descriptions of what people across the globe do when confronted with selfish and beneficent options.*
>
> (Hauser, 2006, p. 131)

This suggests we might expect something akin to linguistic variation, that is, systematic differences among cultures based on parametric settings. These parametric settings explain diverse cultural responses in behavior and principles of harming and helping others (Hauser, 2006, p. 129). "All societies have a normative sense of fairness. What varies between cultures is the range of tolerable responses to situations that elicit judgments of fairness. In essence, each culture sets the boundary conditions, by tweaking a set of parameters for a fair transaction" (Hauser, 2006, p. 99). For Hauser (2006, p. 121), our moral judgments also reflect "intuition percolating up from unconscious and inaccessible principles of action."

Hauser's work thus suggests we have a moral faculty that leads us to judge situations based on notions of fairness. This moral faculty is modeled after innate grammar: there are both strong and weak forms. The strong or nativist form argues that all content (rules, values, meaning, application) is innate. The weak form posits that a general principle is combined with some acquisition mechanism, which in turn provides content specificity. A hybrid form would argue that some content is innate, but other content is acquired.[68] This makes the universal moral grammar a "theory about the suite of principles and parameters that enable humans to build moral systems. It is a toolkit for building a variety of different moral systems as distinct from one in particular. The grammar or set of principles is fixed, but the output is limitless within a range of logical possibilities" (Hauser, 2006, p. 300).

When applied to moral behavior, moral principles may be gleaned from anthropological sources. For instance, the edict "thou shall not kill" is a principle holding of many religions. Yet, killing in the form of infanticide or honor killing is accepted by some cultures. These are exceptions to the rule. Hauser's moral faculty approach holds that examples of killing are permissible deviations (parametric settings according to culture). Thus, Hauser accounts for societal and cultural variation of norms by positing an absolute norm that is universal but with local departures based on specific sociohistorical conditions. "Underlying the extensive cross-cultural variation we observe in our expressed social norms is a universal moral grammar that enables each child to grow a narrow range of possible moral systems. When we judge an action as morally right or wrong, we do so instinctively, tapping a system of unconsciously operative and inaccessible moral knowledge. Variation between cultures in their expressed moral norms is like variation between cultures in their spoken languages. Both systems enable members of one group to exchange ideas and values with each other, but not with members of another group" (Hauser, 2006, p. 420). "To say that we are endowed with a universal moral grammar is to say that we have evolved general but abstract principles for deciding which actions are forbidden, permissible, or obligatory. There are no principles dictating which particular sexual, altruistic, or violent acts are permissible" (Hauser, 2006, p. 420).

MORAL PSYCHOLOGY AND NEUROSCIENCE

Related advances in moral psychology also shed light upon the substrates of moral behavior in human evolution and its legacy on the neuroscientific level. Building on Robert Trivers and Edward O. Wilson, several research programs have converged upon results lending support to the moral sense hypothesis as features of the pressures of natural selection upon our human ancestors.[69] More specific findings about the emotional role provided in moral behavior pinpoints the ventromedial prefrontal cortex (VMPC), especially as assessed by tests of moral cognition of patients subject to VMPC damage. (Research into the neural basis of perceived fairness reveals that fairer offers in game-based experiments lead to greater activity in the ventral striatum, the VMPC, and the left amygdala, areas known to be "reward centers." Reactions against unfairness also have physiological markers, such as increased skin conductance.) Cooperation can provoke similar neural reward responses. Charitable donations similarly seem tied to frontal mesolimbic structures, relying upon two parallel reward systems, one linking the ventral segmental area with mesolimbic areas and the ventral striatum (typically involved in pecuniary reward) and one including the subgenual area for donations. This is noteworthy since the subgenual area (at the nexus of the posterior part of the medial orbitofrontal cortex, the ventral cingulated cortex, and septal region) is tied to social attachment in both humans and other animals. Decisions to donate similarly have their roots in measured compassion and anger. The opposition to donation had its own network of brain regions, comprising a network between the lateral orbitofrontal cortex, the anterior insula, and the dorsolateral cortex; some of these have been previously implicated in the experience of disgust.

Altruism has often been linked to empathy, and the neural mechanisms of empathy appear to be recruited for altruistic feelings. Perceiving the actions and intentions of others has been found to involve the posterior superior temporal cortex, particularly in the right hemisphere; variable activity in these regions has been linked to variation in levels of self-reported altruism. Empathy itself also has correlates in the cerebral cortex; its perspective-taking manifestation results in activation of middle insula, anterior mid-cingulate cortex (aMCC), medial, and lateral premotor areas, and selectively in left and right parietal cortices.

Additional studies have implicated key brain structures contributing to moral affect. When these are personal dilemmas in which danger or moral violation happens to immediate subjects, heightened activity arises in the medial frontal gyrus, posterior cingulate gyrus, and the bilateral superior temporal sulcus, while impersonal dilemmas activate more "working memory" segments, including the dorsolateral prefrontal cortex and the parietal cortex. Hormonal elements likewise appear to support a human "moral sense," particularly that of oxytocin, the presence of which encourages trust in others, as well as generosity. The roots of oxytocin in human physiology also are clear for vicariously witnessing "morally elevating" stimuli. (Breastfeeding women seeing a morally uplifting video were more likely to nurse their babies.)

Recent work in social psychology also lends credence to elements of a moral sense. For example, in constructing his social intuitionist model of moral judgment, Jonathan Haidt acknowledges his debt to moral sense theorists: "Where do moral beliefs and motivations come from? They come from sentiments which give us an immediate feeling of right and wrong, and which are built into the fabric of human nature. Hume's answer is our answer too."[70] Haidt's social intuitionist model draws upon previous work in social psychology pointing to a "dual process" system in which an "intuitive" system responds quickly, effortlessly, and automatically, with its contents seldom available to introspection, and affectively laden. A second system is more ponderous, deliberate, linear, and devoted to serial reasoning, with limited computing power to bear on immediate objects of attention. The relative inaccessibility of such automatic processes to conscious thought and the contribution of such automatic processes to moral behaviors like altruism have been previously documented, and they have provided the groundwork for social intuitionist models and experiments. (Haidt suggests the affective system is what leads in moral judgments and that much of what is deemed "moral reasoning" à la Kant and Kohlberg is often actually post hoc rationalizing of judgments already made.) If moral reasoning does enter into the process, it is secondary.

CONCLUSION

This chapter summarizes evidence from a wide range of disciplines supporting the idea of an innate moral sense. Empirical evidence from a wide range of fields supports the claim that people have an innate ethical framework, much as we have an innate predisposition for language. Mother Nature may encode ethical content on our ethical framework, predisposing us toward certain moral choices. The range, direction, and extent of this predisposition is far from clear, and I am not arguing that moral sense theory is the definitive moral theory. Nonetheless, the analysis presented here does matter since arguments derived from utilitarianism and modern economics suggest humans adopt a calculative prompting of self-interest. Kantian approaches further suggest a role for obeying categorical rules. Both moral sense theory and my own empirical work on moral choice draw attention to an alternative to these two important ethical theories.

Empirically grounded theories provide scientific evidence about how it is humans are prompted to be moral, not why they should be moral. These are large and important questions, and ethicists should be addressing them using all the evidence of science at their disposal. By drawing attention to the possible sources of moral intuitions and innate drives to act morally and thinking about the theoretical implications of works related to moral sense theory, the intellectual payoff is clearly evident.

ENDNOTES

1. Vilfredo Pareto (1848–1923) was an Italian economist, engineer, philosopher, and sociologist. Best known for introducing the concept of Pareto efficiency, Pareto helped developed the field of microeconomics by making important contributions to the study of income distribution and the analysis of how individuals make choices. I do not remember where I heard this story but believe it may have been Robert Fogel who told it to me.
2. Parts of this chapter appeared in *Ethics in an Age of Terror and Genocide* (Monroe, 2012). I am grateful to Princeton University Press for their permission to reprint this argument here.
3. I am using culture, society, time, etc., interchangeably. A full discussion of the differences lies beyond the space constraints of one chapter and is not necessary for the purposes of our discussion of the particular topic of this volume.
4. I use the terms "ethics" and "morality" interchangeably, both because this is the common practice in everyday language and because there is no one commonly accepted distinction among the scientists working in the diverse fields we have discussed here. Nonetheless, there are basic, albeit subtle, differences that moral philosophers or ethicists would recognize. In general, morals refer to personal character, while ethics tends to refer to a social system in which those personal morals are applied. This means "ethics" tends to point to standards or codes of behavior expected by the group to which individuals belong. Further discussion of the myriad other intricate subtleties lies beyond the scope of this chapter.
5. Other theorists—from Plato to Arendt—often allude to elements of moral sense theory. The description just presented focuses on theorists who explicitly concentrated on the theory and identified themselves as moral sense theorists. Late Enlightenment thinkers found much to criticize in moral sense theory. These critiques cluster in four areas.
   (1) *Feelings and a moral imperative*. Critics argued that there is more to morality than feeling and that a feeling, as such, cannot create a moral imperative to action. They argued, further, that the mark of moral responsibility is the actor's freedom to reach a moral judgment and to choose a moral course of action. Given this, they find moral sense theory reduces the human being to an instrument of his own dispositions if the moral dimensions of life arise by sentiments, and if "right" and "wrong" are only the consequences of a kind of emotional reflex over which the moral agent has little control.
   (2) *Reason* versus *emotions*. Closely related to this critique is Kant's (1797/1991) argument that if an action is impelled by any desires emanating from the psychological or biological facts of life, then it is determined by these factors and cannot be considered moral at all. Hence, as rational beings—this criticism continues—we occupy the "intelligible" realm, and actions are determined in this realm not by causes but by reasons. Actions are morally right to the extent that they instantiate a moral maxim.
   (3) *Sentiment* versus *reasoned judgment of worthiness of the sentiment*. Critics who grant that the moral side of life does include emotions—such as anger and love—raise a further question: Does moral action have to do just with the emotions themselves? Is not the object to which we feel emotionally disposed also relevant? In other words, should not the critical issue be more than *just* the sentiments of approval or approbation but also the *judgment* of what and who deserves such attitudes and feelings? This view also argues that such judgment comes from deliberative processes and, therefore, the moral life cannot be separated from reason.
   (4) *Resolving difference in innate moral senses*. Finally, critics ask about the difficulties in resolving different moral senses. If morality is determined by sentiment and feelings, and does not reflect any objective state in the world, what happens when these feelings vary from person to person? How are these disputes resolved? By reason? Force? Convention? By what is evolutionarily adaptive? If the moral sense is a feeling common to all, then these moral sentiments should retain a kind of objectivity. Even if they do not reflect anything in the universe apart from human feelings, our moral judgments may be true or false, depending on whether they capture the universal human moral sentiment. But, if feelings vary from one individual to the next, moral judgments become entirely subjective, leaving no acceptable way to adjudicate competing moral claims. Alternative choices and preferences may be irreconcilable.

   How does moral sense theory propose to resolve such disagreements?
6. Porter (2001).
7. Myers (1985).
8. This school included Francis Hutcheson, Anthony Ashley Cooper (aka the third Earl of Shaftesbury), Adam Smith, Bishop Butler, and David Hume as its best known advocates. While these men did not always agree on fundamental principles, they nonetheless shared a common outlook that distinguishes them from other ethicists.
9. Shaftesbury (1699/1977).
10. Hutcheson's ethical theory is expressed in three works: *Inquiry into the Original of Our Ideas of Beauty and Virtue* (1725/1971), *An Essay on the Nature and Conduct of the Passions and Affections, With Illustrations upon the Moral Sense* (1728/1969), and *System of Moral Philosophy* (1755/1968). First written in 1738, this book was expanded and revised throughout Hutcheson's life and published after his death. It contains the fullest expression of Hutcheson's philosophy, ranging from discussions of our human nature,

duties to God and to each other, the rights and duties of parents, civil liberty, rights and contracts, and laws of peace and war. It contains an argument against slavery that was influential in providing academic legitimacy to the anti-slave movement. Reprinted in colonial Philadelphia, it supposedly influenced authors of the US Constitution.

11. Smith (1759).
12. Smith maintains the basis of morality in the sentiment but moves toward the device of an impartial spectator. He thus shifts from reliance on an innate moral sense and is not considered a moral sense theorist. Other, more minor moral sense theorists, however, such as Joseph Butler, emphasized harmony between morality and enlightened self-interest, though Butler claims that happiness is a by-product of the satisfaction of desires for things, not just the desire for happiness in and of itself. Such direct and simple egoism was a self-defeating strategy for Butler, who argued that egoists would do better for themselves if they adopt immediate goals other than their own interests and then live their everyday life in accord with these more immediate goals.
13. Hume (1777/1978, 1999).
14. Piaget (1932), Kohlberg (1981, 1984).
15. DeWaal (1986, 2001), Goodall (1986, 1990).
16. See Monroe et al. (2009) for a review.
17. Hume's emphasis on the consequence of an act as the test of morality, however, was accepted by many theorists. Hence the split between deontologists and consequentialists.
18. Marx and Engels (2004).
19. Wittgenstein (1963).
20. Rawls (1971).
21. See Geertz (2001) on the debate over observer contamination and fabricated data in anthropology. The 2010 investigation into the reliability of Marc Hauser's empirical work is one illustration of the general criticisms of this work but should not call into question the reliability of the entire field.
22. Moral sense theory, as generally construed, assumes it is grounded in sentiments or emotions. Hence, our basic sense of what is good or bad is neither inferred from nor based upon any propositions. Such non-inferential moral knowledge is based on a priori non-empirical knowledge such as mathematical truth. What is often referred to as "ethical intuitionism" is distinguished from moral sense theory and is said to model the acquisition of such non-inferential knowledge about right and wrong on empirical grounds, in the manner that we acquire knowledge of the color of objects. Since our interest here is not in constructing an extended discussion of the concept of morality, we define it simply as behavior designed to further the well-being of others. See Monroe (2004) for fuller discussion.
23. Piaget (1932).
24. Kagan (1981).
25. Kohlberg (1976).
26. Gilligan (1982).
27. See Monroe (1996) for a discussion of such work.
28. Kagan (1981, 1989), Kagan et al. (1979), Kagan and Lamb (1987).
29. While Kagan finds no English word for this concept and refers to it as virtue, his elaboration on this consonance appears to correspond closely to what Freud called the super-ego.
30. Research dating from the 1950s found that mice that had stimulus applied to the pleasure centers of their brains would ignore food in preference for behavior that triggered such stimuli. See *Inside the Animal Mind* for a fascinating, visual overview of these experiments, which includes excerpts from experiments on many kinds of animals, not just laboratory mice.
31. This resembles Smith's concept of empathy in many regards.
32. Malcolm Gladwell, Books, "Baby Steps," *The New Yorker*, January 10, 2000, p. 80.
33. The entire discussion is directed at what might be considered the normal pattern and ignores pathology or extremes.
34. Kagan (1998, p. 175).
35. "What is biologically special about our species is a constant attention to what is good and beautiful and a dislike of all that is bad and ugly. These biologically prepared biases render the human experience incommensurable with that of any other species" (Kagan, 1998, p. 191). Kagan does not discuss the link between moral superiority of humans and keeping slaves. "The biological imperative for all animals is to avoid hunger and harm and to reproduce, and adult chimps spend much of each day doing just that. But humans in ancient societies established cities, wrote laws forbidding certain behaviors, built ships, wore finery, used slaves, attended plays, and, in Greece, admired the Parthenon."
36. Darwin (1889).
37. Wilson's APSA Presidential address and his subsequent book were an exception. Wilson (1993, p. 13) asked whether "people everywhere have a natural moral sense that is not entirely the product of utility or convention." Wilson defined moral sense as "a directly felt impression of some standards by which we ought to judge voluntary action. The standards are usually general and imprecise. Hence, when I say that people have a moral sense, I do not wish to be understood as saying that they have an intuitive knowledge of moral rules. Moral rules are often disputed and usually in conflict; but the process by which people resolve those disputes or settle those conflicts leads them back to sentiments that seem to them to have a worth that is intuitively obvious" (1993, p. 13). Unfortunately, Wilson's own demonstration of a moral sense left much to be desired. We need greater specificity and testable ideas for political scientists to reexamine moral sense theory as a plausible account of moral behavior.
38. Dawkins (1976).
39. DeWaal (1986), Goodall (1986).
40. Hauser (2006).
41. Rawls (1971).
42. Crawford (1937), DeWaal (1982).
43. Bonnie and DeWaal (2004).
44. In one experiment, for example, a monkey called Sammy was in such a hurry to get her food reward that she released the tray before her coworker (Bias) got her reward. When Bias realized that her tray had bounced out beyond her reach, she screamed. Sammy then approached her own pull bar and released it so Bias could get Bias's cup of food. Sammy did so despite the fact that her own food cup was now empty (DeWaal, 1986).
45. Brosnan and DeWaal (2003).
46. See *Animal Spirits* by Akerloff and Schiller (2009) as one illustration of this work.

47. Clark and Grote 2003, Smaniotto (2004), Brosnan et al. (2005).
48. Range et al. (2009).
49. See DeWaal (2001) for arguments on animal culture and 1982, 1996 on animal emotions.
50. DeWaal's (2001) most recent work focuses more on the ability of animals to learn behavior, much as humans do, but since that is not directly relevant to my argument here, I do not pursue the line of inquiry it suggests about the possibilities of shaping the moral sense.
51. Interestingly, Kagan also notes this phenomenon in very young children (Kagan, 1984).
52. DeWaal notes the example of two chimpanzees who did not come when they were called by their keepers at feeding time. Because these two stayed out late, the other members of the group were not fed at the normal feeding time, and the entire group remained hungry. The rest of the group retaliated, and beat the two miscreants. The next night, these two were the first to come in at feeding time, and they never again dallied when called for food (1996, p. 89).
53. See Goodall (1986, 1990), Sapolsky (2002).
54. DeWaal, himself, raises a further possibility by suggesting morality ought to be universal and holistic. Other primatologists do not go this far in their argument, however, and I am not making such a claim here, even though such an argument could plausibly be made (see DeWaal et al., 2009).
55. Gintis (2003).
56. Axelrod (1984).
57. Trivers (1971).
58. Such results corroborate "public goods" experiments such as that of Fehr and Gachter (2002).
59. See work by Bruno Frey and Alois Stutzer (2001) entering happiness into the economic calculus or Amatrya Sen's creative work on introducing the concept of capabilities into our estimates of a nation's wealth.
60. See Chomsky (1965) for the distinction between competence and behavior.
61. Ironically, the main proponent of this approach—Marc Hauser—refers neither to the original work on an innate moral sense nor to Kagan's work.
62. Hauser (2006), Young et al. (2007).
63. Hauser (2006).
64. Hauser focuses on traditional perspectives of morality as they confront archetypal moral dilemmas. He then outlines three main moral philosophical approaches: the Kantian, Humean, and Rawlsian perspectives. (Hauser ignores the extent to which Rawls's work is based on Kant's.) He finds strong forms of Kantian and Humean moral philosophy unable to account for the diverse behavior of those entangled in moral quandaries.
65. Damasio (1994, 1999), Kahneman and Tversky (2000).
66. "Reasoning and emotion play some role in our moral behavior, but neither can do complete justice to the process leading up to moral judgment." Hauser (2006, p. 11).
67. Hauser blends evolution and moral psychology, classifying Piaget and Kohlberg as Kantian and arguing (1) that neither psychologist offers a convincing account of how children or adults move from one stage to the next and (2) that both psychologists conflate correlation with causation. Thus, while Hauser finds their stage theories of moral development interesting, he finds both theorists offer a map rather than a progression of moral development.
68. Hauser seems to favor three models of the Rawlsian creature: weak, temperate, and staunch. He considers these as phenotypic expressions of a genetic potential set in different contexts. A weak Rawlsian "as a species, distinct from all others … has the capacity to acquire morally relevant norms, but nature hasn't provided any of the relevant details" (2006, p. 198). A temperate Rawlsian is "equipped with a suite of principles and parameters for building moral systems. These principles lack specific content, but operate over the causes and consequences of action" (2006, p.198). Finally, the staunch person "is equipped with specific moral principles about helping and harming, genetically built into the brain and unalterable by culture" (2006, p. 199).
69. See Monroe (2012) for full citations of this work.
70. Haidt and Bjorklund (2008, p. 185)

REFERENCES

Ackerloff, G., Schiller, R.J., 2009. Animal Spirits: How Human Psychology Drives the Economy, and Why It Matters for Global Capitalism. Princeton University Press, Princeton, NJ.

Axelrod, R., 1984. The Evolution of Cooperation. Basic Books, NY.

Bonnie, K.E., DeWaal, F., 2004. Primate social responsibility and the origin of gratitude. In: Emmons, R.A., McCullough, M.E. (Eds.), The Psychology of Gratitude. Oxford University Press, Oxford, pp. 213–229.

Bowles, S., Gintis, H., 2002. Prosocial Emotions. Santa Fe Institute Working Paper #02-02-028.

Bronson, S.E., DeWaal, F., 2003. A proximate perspective on reciprocal altruism. Human Nature 13, 129–152.

Bronson, S.E., Schiff, H., DeWaal, F., 2005. Tolerance for inequity increases with social closeness in chimpanzees. Proceedings of the Royal Society B 272, 252–258.

Chomsky, N., 1965. Syntactic Structures. Mouton, The Hague.

Clark, M.S., Grote, N.K., 2003. Close relationships. In: Milton, T., Lerner, M.J. (Eds.), Handbook of Psychology: Personality and Social Psychology. Wiley, NY, pp. 446–461.

Crawford, M., 1937. The cooperative solving of problems by young chimpanzees. Comparative Psychology Monographs 14, 1–85.

Damasio, A., 1994. Descartes' Error: Emotion, Reason, and the Human Brain. Putnam, NY.

Damasio, A.M., 1999. The Feeling of What Happens: Body and Emotions in the Making of Consciousness. Harcourt Brace, New York.

Darwin, C., 1889. The Origin of Species. Appleton, NY.

Dawes, C., Fowler, J., Johynson, T., et al., 2007. Egalitarian motives in humans. Nature 446, 794–796.

Dawkins, R., 1976. The Selfish Gene. Oxford University Press, NY.

DeWaal, F., 1982. Chimpanzee Politics: Power and Sex among Apes. Revised edition 1998. Johns Hopkins University Press, Baltimore.

DeWaal, F., 1986. The integration of dominance and social bonding in primates. Quarterly Review of Biology 61 (4), 459–479.

DeWaal, F., 2001. The Ape and the Sushi Master. Cultural Reflections of a Primatologist. Basic Books, NY.

DeWaal, F., Macedo, S., Ober, J., 2009. Primates and Philosophers: How Morality Evolved. Princeton University Press, Princeton, NJ.

Fehr, E., Gachter, S., 2002. A theory of fairness, competition, and cooperation. Quarterly Journal of Economics 114, 817–868.

Frey, B., Stutzer, A., 2001. Happiness and Economics: How the Economy and Institutions Affect Human Well-being. Princeton University Press, Princeton, NJ.

Geertz, C., 2001. "Life among the Anthros." Book review of Patrick Tierney's Darkness in El Dorado: how scientists and journalist devastated the Amazon. New York Review of Books 48 (2), 18–21.

Gilligan, C., 1982. In a Different Voice: Psychological Theory and Women's Development. Harvard University Press, Cambridge, MA.

Gintis, H., 2003. The Hitchhiker's guide to altruism: genes, culture and the internalization of norms. Journal of Theoretical Biology 220 (4), 407–418.

Goodall, J., 1986. The Chimpanzees of Gombe: Patterns of Behavior. Belknap Press of Harvard University Press, Cambridge, MA.

Goodall, J., 1990. Through a Window: My Thirty Years with the Chimpanzees of Gombe. Houghton Mifflin, Boston.

Haidt, J., Bjorklund, F., 2008. Social intuitionists answer six questions about moral psychology. The Cognitive Science of Morality. In: Sinnott-Armstrong, W. (Ed.), Moral Psychology, vol. 2. MIT Press, Cambridge, MA, pp. 181–217.

Hauser, M., 2006. Moral Minds: How Nature Designed Our Universal Sense of Right and Wrong. Ecco, NY.

Hume, D., 1777/1978. In: Nidditch, P.H. (Ed.), Enquiries Concerning Human Understand and Concerning the Principles of Morals. Clarendon, Oxford.

Hume, D., 1999. An Inquiry into the Original of Our Ideas of Beauty and Virtue. Garland, New York. Published originally in 1725.

Hutcheson, F., 1715/1971. Inquiry into the Original of Our Ideas of Beauty and Virtue. Garland, New York.

Hutcheson, F., 1728/1969. An Essay on the Nature and Conduct of the Passions and Affections, With Illustrations Upon the Moral Sense. Scholars' Facsimile and Reprints, Gainesville, FL.

Hutcheson, F., 1755/1968. System of Moral Philosophy. A. M. Kelley, New York.

Kagan, J., Lamb, S. (Eds.), 1987. The Emergence of Morality in Young Children. University of Chicago Press, Chicago.

Kagan, J., et al., 1979. A Cross-Cultural Study of Cognitive Development. University of Chicago Press, Chicago.

Kagan, J., 1981. The Second Year: The Emergency of Self-Awareness. Harvard University Press, Cambridge, MA.

Kagan, J., 1984. The Nature of the Child. Basic Books, New York.

Kagan, J., 1989. Unstable Ideas: Temperament, Cognition, and Self. Harvard University Press, Cambridge, MA.

Kagan, J., 1998. Three Seductive Ideas. Harvard University Press, Cambridge, MA.

Kahneman, D., Tversky, A., 2000. Choices, Values and Frames. Cambridge University Press, NY.

Kant, I., 1797/1991. The Metaphysics of Morals. Introduction, Translation, and Notes by Mary Gregor. Cambridge University Press, Cambridge.

Kohlberg, L., 1976. Moral stages and moralization: the cognitive developmental approach. In: Likona, T. (Ed.), Moral Development and Behavior. Holt, Rinehart and Winston, New York, pp. 31–53.

Kohlberg, L., 1981. Essays on Moral Development. Harper and Row, San Francisco.

Kohlberg, L., 1984. Essays on Moral Development, vol. 2. Harper and Row, NY.

Locke, J., 2000. John locke: an essay concerning human understanding. In: Fuller, G., Stecker, R., Wright, J. (Eds.), Routledge Philosopher in Focus Series. Routledge, London.

Markey, S., September 17, 2003. Monkeys Show Sense of Fairness, Study says. National Geographic News.

Marx, K., Friedrich, E., 2004. The Communist Manifesto. Barron's, Hauppauge, NY.

Monroe, K., 2004. The Hand of Compassion: Portraits of Moral Choice During the Holocaust. Princeton University Press, Princeton, NJ.

Monroe, K.R., Martin, A., Ghosh, P., 2009. Politics and an innate moral sense: scientific evidence for an old theory? Political Research Quarterly (September) 62, 614–634.

Monroe, K.R., 1996. The Heart of Altruism. Princeton University Press, Princeton, NJ.

Monroe, K.R., 2012. Ethics in an Age of Terror and Genocide. Princeton University Press, Princeton, NJ.

Myers, M., 1985. The Soul of Modern Economic Man: Ideas of Self-Interest, Thomas Hobbes to Adam Smith. University of Chicago Press, Chicago.

Piaget, J., 1932. The Child's Conception of Numbers. Routledge and Kegan Paul, London.

Porter, R., 2001. The Enlightenment. Macmillan, NY.

Range, J., et al., 2009. The absence of reward induces inequality aversion in dogs. Proceedings of the National Academy of Sciences 106 (1), 340–345.

Rawls, J., 1971. Theory of Justice. Oxford University Press, Oxford.

Sapolsky, R., 2002. A Primate's Memoir. Touchstone Books, NY.

Shaftesbury, 3rd Earl of (Anthony Ashley-Cooper), 1699/1977. In: Walford, D. (Ed.), An Inquiry Concerning Virtue, or Merit. 1714 Edition With Toland's 1699 Edition and Bibliography. Manchester University Press, Manchester.

Smaniotto, R.C., 2004. You 'Scratch My Back and I Scratch Yours' Versus 'Love thy Neighbour': Two Proximate Mechanisms of Reciprocal Altruism. PhD dissertation. University of Groningen.

Smith, A., 1759/1976. The Theory of Moral Sentiments. Introduction by E.G. West. Liberty Classics, Indianapolis. Originally published in 1759 and 1854.

Trivers, R., 1971. The evolution of reciprocal altruism. Quarterly Review of Biology 46, 35–57.

Wilson, J.Q., 1993. Moral Sense. Free Press, NY.

Wittgenstein, L., 1963. Tractatus Logico-Philosophicus. Routledge and Kegan Paul, London.

Young, L., Cushman, F., Hauser, M., Saxe, R., 2007. The neural basis of the interaction between theory of mind and moral judgment. In: Proceedings of the National Academy of Sciences of America, 104, pp. 8235–8240.

Chapter 46

What HIV Has Taught About the Interactions Between Biology, Culture, and Other Evolving Systems

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THE INTERACTION OF EVOLUTIONARY SYSTEMS

Although our first understanding of the evolutionary process came from biology, we can define evolution more broadly as a gradual process in which something changes into a different and usually more complex or better form. A key to understanding evolutionary systems is the concept of an emergent property as a property of a collection or complex system not present in its component parts. As such, it could not have been predicted ahead of time. A simple example is saltiness, an emergent property of salt, present in neither sodium nor chloride on their own. The field of complexity science categorizes emergent properties into various types (Fromm, 2005) and recognizes such evolutionary processes work at many levels from cosmological, chemical, biological, cultural/political, commercial, scientific/technical/industrial, and regulatory amongst others (Fig. 46.1).

These forms of evolution operate over very differing time frames, and for this reason the emergent properties of older and slower forms of evolution are more likely to exert constraints and selective pressures on more recent or rapidly changing systems than the other way around. This hierarchy in no way implies the greater importance of one field over another but rather may provide guidance of the likely dominant directionality of the influences.

Life on earth is estimated to have begun about 3.5 billion years ago, marking the beginning of biologic evolution. A critical threshold was the emergence of language and collective learning that has only developed in man in the last 250,000 years. This has underpinned downstream evolutionary processes that have further accelerated the appearance of additional emergent properties.

Biological evolution has provided solutions to improve survival and reproductive success, and this has imbued us with strong instincts to nurture our families and insiders and defend against external threats. These instincts were selected for by threats that could be defended, or opportunities that could be exploited, in our environment when we were hunter-gatherers. As efficient as these evolutionary processes are at providing solutions to modifiable threats or exploitable

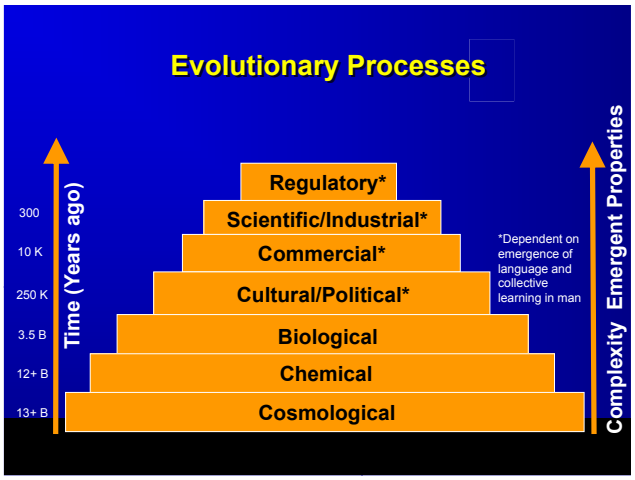

FIGURE 46.1 The pyramid of evolutionary processes: The universe has become increasing complex since its formation over 13 billion years ago. Out of this complexity, new properties have emerged such as language and collective learning in man over the last 250,000 years. This has critically underpinned cultural and other evolutionary processes that shape our world today.

On Human Nature. http://dx.doi.org/10.1016/B978-0-12-420190-3.00046-6

opportunities in our environment, they do so without simultaneously providing a rationale for why the solution worked. In other words, the human brain is highly adapted, individually and collectively, to empirically solve such problems in our environment, but we are prone to assign an erroneous post-hoc explanation for our success. This may cause a problem at a later time if we act on such assumptions. In contrast, the more painstaking, strictly logical, and deterministic scientific process, a more recent emergent system in evolutionary terms, provides understanding of how things work to facilitate design of solutions.

Language, collective learning, agriculture, industrialization, and globalization have also emerged as solutions to needs of our species, mitigating many of the modifiable threats of our hunter-gatherer past that shaped our instincts. These emergent properties have underpinned our accelerating collective progress and rendered some of our more primitive instincts, such as excessive food-seeking and other addictive behaviors, aggression, paranoia, anxiety, and similar traits unnecessary or maladaptive for most aspects of everyday life today (Fig. 46.2). Commercial and political evolutionary processes can very effectively find and exploit such instincts in an evolutionary arm race for profit as exemplified by the excesses evident in many of the most successful contemporary foods, computer games, social media, sports, entertainment, literature, media, and political strategies.

We have an instinct to move to safe, resource rich settings. Remarkably we live in one of the first generations in which the mass voluntary movement of people has become possible. We have therefore witnessed the establishment of remarkable genetic, ethnic and culture heterogeneity in the developed world and a major translocation of nearly 2 billion people from rural into urban centers in emerging nations. In our time, the basic needs of more people have been met, trade and globalization has increased, and information has come to flow more freely. Altruistic cultural mores have emerged as we have enjoyed an unprecedented period of safety, affluence, and relative peace. Unfortunately, we may not be free to enjoy this as the products of intense cultural and commercial evolution exploit more primitive instincts of old to recreate an environment that often feels as threatening as that of our hunter-gatherer past.

So, what can HIV teach about the interacting evolutionary systems that shape our world? Specifically, why did the HIV pandemic emerge when and where it did, and what can be learned from our response to HIV that might guide our response to other global challenges.

Why Did the HIV Pandemic Emerge When and Where It Did?

The chimp virus Simian Immunodeficiency Virus (SIVcpz) was first transmitted to human hunters or bush meat vendors, and mutated into HIV, in Cameroon at the beginning of the last century. Other species of monkey in East Africa have been found to have their own distinct stains of SIV but not get sick or die. Evolving to this mutual accommodation benefitted both the virus and host and gave these monkeys infectious disease missiles with the potential to annihilate a closely related species competing for local resources. It is of no surprise then that HIV, the greatest emerging infectious disease of our time, came from the monkey species most similar to us. We now know that chimps themselves hunted and ate these two smaller species of ape, red-capped mangabeys and greater spot-nosed monkeys, in west central Africa, and the SIVs from those two viruses recombined to create the hybrid virus SIVcpz that could infect their chimp predators and later man (Bailes et al., 2003).

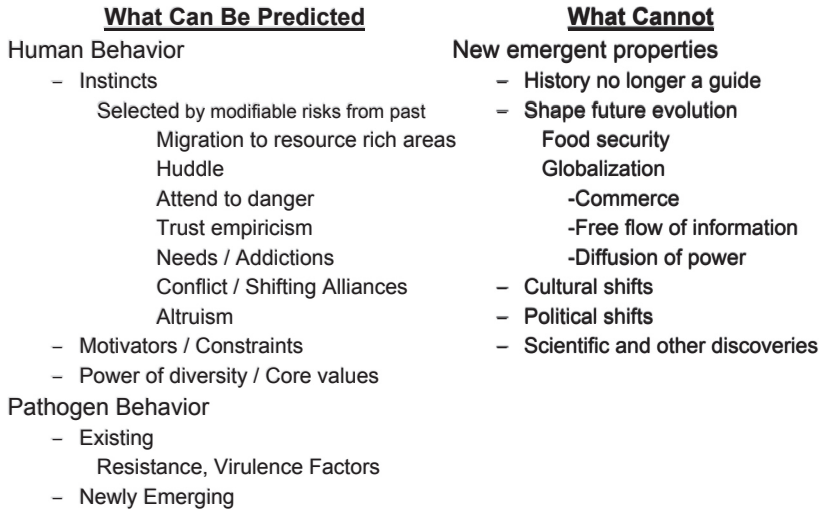

FIGURE 46.2 Predicting the Future: Human and Pathogen Behavior that may been predictable compared to emergent properties that could not have been predicted before they occurred.

Driven by the changes associated with colonialism, HIV is believed to have spread from the Cameroon from the 1920s by road, rail, and river links to the rapidly growing population of Kinshasa in the Democratic Republic of the Congo (DRC) and beyond (Faria et al., 2014). Demographic, cultural, and economic changes also drove increased sexual promiscuity and prostitution with an associated increase in the prevalence of sexually transmitted diseases, which are known to substantially increase the risk of transmission of HIV. Haitian professionals who went to the DRC in the 1960s probably carried the virus back to Haiti in 1964 before a single migration of HIV to the United States is believed to have occurred around 1969 (Gilbert et al., 2007). The rare cancer Kaposi's Sarcoma and infection *Pneumocystis jiroveci* pneumonia were first recognized in homosexual men with low $CD4^+$ T cell counts in New York and California in 1981 (Gottlieb, 1981). These and other unusual opportunistic infections and malignancies were used to define the Acquired Immunodeficiency Disease Syndrome (AIDS) in 1982, and before long, it was apparent the AIDS epidemic was spreading among hemophiliacs and others receiving blood products, intravenous drug addicts, and the infants of those with the syndrome.

There was much initial speculation as to the cause of AIDS until HIV was identified in 1983 (Gallo et al., 1983; Barré-Sinoussi et al., 1983). Why did this take so long? First, there is a latency period of several years between silent infection with HIV and the development of symptomatic AIDS. Second, unlike other viral epidemics such as Ebola, influenza, or SARS, standard laboratory tools of the time could not detect the virus. HIV antibody testing became available in 1984 allowing the identification of HIV-infected individuals before they developed AIDS.

MHC Coevolution With Herpes and Other Viruses

The herpes viruses are large DNA viruses that share more than 100 million years of coevolution with current hosts and have hitched their survival to the particular species they infect (McGeoch et al., 2006). The eight human herpes viruses (Herpes Simplex-1 and -2, varicella zoster, Epstein–Barr, cytomegalovirus, and human herpes virus-6, -7, and -8) have different primary target cells and sites of latency and are very efficient at establishing chronic infection (Virgin, 2009). Herpes and other DNA viruses coadapted with their vertebrate host are known to possess genes encoding molecules that show evidence of homology to molecules of their hosts presumably as a result of horizontal gene transfer (Barry and McFadden, 1997; Lalani and McFadden, 1999).

For most of our evolution, these lifelong infections were acquired early in life, and it has been proposed they provide broadly protective immunodominant epitopes and a form of natural immunization (Chiu et al., 2014). For example, the pp65 protein of rhesus cytomegalovirus (CMV) generates a T cell response that vigorously restricts viral replication during primary infection but has little impact on viral shedding. This appears to be an example of a viral protein that has evolved to benefit a chronic persistent virus by facilitating an acute immune response to avoid overwhelming the host in primary infection, while providing the host long-term benefit at an individual and population level (Malouli, 2014). This symbiotic coevolution has been disrupted since industrialization as infections such as Ebstein–Barr virus (EBV) are acquired later in life in the developed world, and it has been proposed that this is responsible for the increasing incidence of allergy and autoimmune conditions such as multiple sclerosis (Shapira et al., 2010).

The extraordinary polymorphism of major histocompatibility complex (MHC) Class I and II alleles provides protection to infectious diseases at a population level, but the individual only inherits a very limited MHC repertoire. So although every individual in the population inherits the same potential to generate the enormous number of different T cell receptors, the functional T cell repertoire is limited to those cells with T-cell receptors (TCRs) that bind the self HLA-peptide complexes present in the individual with moderate but not high affinity (Bontrop et al., 1995). The individual's human leukocyte antigen (HLA) Class II restricted T cell help, in turn, shape the B-cell repertoire and HLA Class I restricted T cell cytotoxicity.

The key event resulting in the evolution of the molecular components of antibody, TCR, and MHC molecules is believed to have occurred at the base of the jawed vertebrate evolution about 500 million years ago (Flajnik and Kasahara, 2010; Kaufman, 2010). Binding of functionally important and conserved epitopes in vertebrate proteins and chronic persistent infections such as herpes viruses has therefore shaped MHC and TcR coevolution. This phylogeny appears to be recapitulated in T cell ontogeny, where TCRs are first positively selected according to their capacity to recognize the functionally important and conserved host peptide bound by the particular HLA alleles inherited by the individual, and then further activated by conserved but subtly different epitopes from herpes viruses that bind to those same HLA alleles. Some TCR clonotypes are known to be produced more efficiently during V(D)J recombination (Venturi, 2006). This convergent TCR recombination is believed to contribute to the efficient production of TCR receptors that recognize immunodominant herpes epitopes in CMV and EBV. The HLA molecules are also tuned to efficiently recognize evolutionarily conserved and functionally important epitopes. Specifically, the HLA-A alleles and the HLA- B57/58 group target conserved elements of human herpes viruses and the human proteome most efficiently, while the HLA-B alleles target conserved elements of most RNA viruses, such as HIV, well (Hertz et al., 2011).

Human herpes virus infections facilitate the transmission of HIV and its replication in activated CD4 T cells. HIV infection, in turn, depletes CD4 T cells over time, which ultimately results in severe herpes simplex virus (HSV), CMV, EBV, and Kaposi's sarcoma-associated herpesvirus (or human herpes virus-8)-related AIDS diseases. Phylogenetic modelling that allows the strength of natural selection to vary across the viral phylogeny and gene alignment suggests that, after HSV-1 and chimp herpes virus (ChHV) co-diverged around 6 million years ago, ChHV was transmitted back to an ancestor of humans around 1.6 million years ago (Wertheim, 2014). Many HLA-restricted epitopes are shared between HSV-1, HSV-2, and ChHV, and many MHC alleles have been conserved between chimp and man. Similarly, human and chimp CMV are relatively conserved. For example, the HLA-DR7 restricted CMV epitope DYSNTHSTRYV (DYS) is completely conserved in humans and chimps, and human DYS-specific $CD4^+$ T cells not only recognize, and make an inflated response to, the epitope when presented by HLA-$DR7^+$ human cells but also recognize peptide-sensitized Patr-$DR7^+$ chimpanzee LCL (Elkington et al., 2004). The Patr-DR7 β chain differs from HLA-DR7 at only three amino acid residues. SIV and HIV productively infect and replicate in activate CD4 T cells, and infected cells are killed by cytotoxic T cells, and therefore SIVs have been adapting to the common prevalent MHC-restricted immune responses for at least 32,000 years. We can therefore surmise that when SIVcpz was transmitted to man, it found a favorable landscape of immunogenetics, coinfections, and prevalent immunodominant $CD4^+$ and $CD8^+$ T cell responses in the rapidly growing population in Kinshasa and beyond.

The principle of old and slow evolutionary processes setting the context of more recent and rapidly adaptable systems is well illustrated by HIV. The gradual evolution of the MHC over about 500 million years in vertebrates (Flajnik and Kasahara, 2010; Kaufman, 2010) and SIV over at least 32,000 years (Worobey et al., 2010) contrasts with HLA-restricted cytotoxic T cell selection of HIV escape mutations that can be observed within days of acute HIV infection (Price et al., 1997) and HIV adaptation to HLA-restricted immune responses at a population level (Moore et al., 2002; Kawashima et al., 2009) and decreased virulence (Payne et al., 2014) that becomes apparent within a few years. On the other hand, despite the enormity of the HIV pandemic over the last 35 years, we are yet to detect an effect of HIV on the distribution of HLA alleles in any population.

ANTIRETROVIRAL THERAPY IN TREATMENT AND PREVENTION

Azidothymidine (AZT or zidovudine), a nucleoside analog reverse transcriptase inhibitor that had been originally been developed as a potential anti-cancer drug, was licensed for the treatment of HIV in 1987. This approval occurred only 25 months after the drug was shown to be active against the virus in the laboratory, and it represents an unprecedented example of accelerated drug development. However, AZT rapidly induced resistance mutations in HIV, and the clinical benefits of monotherapy typically disappeared within 6–18 months. It was only with the advent of potent three-drug combinations in 1996 that durable suppression of HIV and avoidance of resistance became achievable, transforming HIV into a chronic manageable disease for those with access to therapy. Although seemingly self-evident, convincing evidence that treatment of HIV reduces transmission to others was not available until 2011 (Cohen et al., 2011), and in September 2015 the World Health Organization recommended treatment for all as soon after diagnosis as possible.

Preexposure prophylaxis with tenofovir-based ART also has demonstrated efficacy in the prevention of transmission, but availability has been limited in the developing world to date. Long-acting injectable anti-retrovirals such as cabotegravir or rilpivirine are being actively investigated and may find a role in the prevention or treatment of HIV in subjects that cannot access or adhere to contemporary oral ART regimens.

CULTURAL AND POLITICAL CONTEXT AND RESPONSE TO HIV

Denial, fear, and sometimes paranoia had a negative influence on the fight against AIDS in both the developed and developing world. There was limited awareness of AIDS in the early years, and it was 2 years into the epidemic before the first effective public health response was taken in the United States, exclusion of at risk individuals from donating blood. In 1985, Rock Hudson announced he had AIDS, and Elizabeth Taylor became the first celebrity to raise awareness of AIDS and funds for research. Despite knowing that HIV cannot be casually transmitted, Ryan White was barred from attending school in Indiana. In 1987, the United States banned HIV-positive travelers from entering the country. In that same year, activist groups mobilized and demanded more research and accelerated approval of drugs. 1990 was the year of the first gulf war, led by President George Bush senior against the regime of Saddam Hussein. The following year, Magic Johnson announced that he had HIV, doing much to increase understanding and acceptance of HIV. By 1992, HIV/AIDS was openly discussed for the first time at the US presidential conventions; Elizabeth Glaser addressed the Democratic and Mary Fisher the Republican convention. In 1994, Tom Hanks won the best actor Oscar for his role in Philadelphia, playing a lawyer fired because he was HIV-positive.

Denial also had significant negative impact on public health in many parts of the developing world. One of the

most tragic and extreme forms of denial was HIV/AIDS denialism as adopted by Thabo Mbeki during his presidency of South Africa between 1999 and 2008. His administration supported arguments that HIV was not the cause of AIDS and denied antiviral treatment to AIDS patients. His health minister advocated the use of unproven herbal remedies instead. It has been estimated these policies were to blame for more than 330,000 preventable deaths (Chigwedere et al., 2008). It has been proposed that the same tenacious antiestablishment attributes that drove Mbeki to fight Apartheid also contributed to his opposition to mainstream scientific evidence on HIV and ART (Gellman, 2000).

In 2003, President George W Bush led the second gulf war against the regime of Saddam Hussein. In the same year, he announced the President's Emergency Plan For AIDS Relief (PEPFAR) to provide access to prevention, care, and treatment programs in many of the developing countries in most need. In 2009, President Obama ordered 30,000 more troops to Afghanistan. In the same year, his administration authorized the Global Health Initiative with PEPFAR as a central component. As of September 2015, the program continues to support provision of ART to 9.5 million people, 8.9 million male circumcisions, prevention of mother to child transmission, training of healthcare workers, and support of orphans and vulnerable children.

SIZE OF THE HIV EPIDEMIC

In 2014, an estimated 36.9 million people were living with HIV, giving a global prevalence of 0.8%. By then, approximately 78 million people had been infected with HIV, and about 39 million people had died since the beginning of the epidemic.

CURRENT TARGETS AND PRIORITIES TO CONTROL THE HIV EPIDEMIC

UN AIDS has set the ambitious target that by 2020, 90% of all people living with HIV will know their HIV status, 90% of all people with diagnosed HIV infection will receive sustained ART, and 90% of all people receiving ART will have viral suppression. Meanwhile, considerable research efforts continue to develop an effective preventative HIV vaccine and to find a functional cure for HIV that would allow patients to stop their HIV medications. It is hoped that it is not too long before these interventions become part of the multipronged prevention armamentarium that currently includes risk reduction measures, male circumcision, use of HIV medications to prevent infection, and treatment of those already infected to stop others becoming infected.

WHAT CAN BE LEARNED FROM OUR RESPONSE TO HIV?

HIV, like many infectious diseases, primarily afflicts disenfranchised out-groups, and HIV/AIDS has been, and often still is, associated with considerable fear and stigma. The early individual and collective response was often dominated by denial and avoidance, which sometimes progressed to fear, discrimination, and inappropriate actions, such as banning Ryan White from school or travelers entering the United States. However, once individuals became personally touched by the suffering of those they knew, as occurred for Elizabeth Taylor when she saw her friend Rock Hudson dying of AIDS, compassion and altruism triumphed. Although community response from the ground up has always been critical, celebrities, the media, and the arts have also lead the cultural and political evolution necessary for broader mobilization of support and resources. History has repeatedly shown that nations are far better prepared and resourced for war than they are to fight infectious diseases pandemics. It will ever be thus, as individual and collective behavioral adaptations leading to success in physical conflict have long been selected for, while few behavioral solutions could be selected to prevent death from infectious disease in our hunter-gather past.

Our positive cultural and political response also underpinned the subsequent rapid scientific and medical progress (Fig. 46.1). The HIV epidemic has brought together an army of creative and courageous individuals driven by the needs of their time from a broad range of backgrounds. This has resulted in unprecedented collaborative gain as patient and community groups, clinicians, health care systems, public health officials, government, industry, regulators, the media, philanthropists, and many others have worked together. We have seen the same type of broad and compassionate and effective response to the recent Ebola crisis that infects monkeys and other animals in the same belt of Africa from which HIV originated. Those countries and groups that were able to respond rapidly with altruism and compassion have been rewarded with a much lower burden of disease and cost to their economies even though this was not the motivator at the time. HIV and other infectious disease have taught us time and again, "Just trust your better instincts and do the right thing without delay."

ACKNOWLEDGMENTS

The early history of HIV in the United States was provided by Dr. Michael Gottlieb who recognized the first AIDS cases in the United States in Los Angeles in 1981. This work was supported in part by the NIH-funded Tennessee Center for AIDS Research (P30 AI110527).

REFERENCES

Bailes, E., Gao, F., Bibollet-Ruche, F., et al., 2003. Hybrid origin of SIV in chimpanzees. Science 300 (5626), 1713.

Barré-Sinoussi, F., Chermann, J.C., Rey, F., et al., 1983. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS). Science 220 (4599), 868–871.

Barry, M., McFadden, G., 1997. Virus encoded cytokines and cytokine receptors. Parasitology 115 (Suppl.), S89–S110.

Bontrop, R.E., Otting, N., Slierendregt, B.L., et al., 1995. Evolution of major histocompatibility complex polymorphisms and T-cell receptor diversity in primates. Immunological Reviews 143, 33–62.

Chigwedere, P., Seage 3rd, G.R., Gruskin, S., et al., 2008. Estimating the lost benefits of antiretroviral drug use in South Africa. Journal of Acquired Immune Deficiency Syndromes 49 (4), 410–415.

Chiu, C., McCausland, M., Sidney, J., et al., 2014. Broadly reactive human CD8 T cells that recognize an epitope conserved between VZV, HSV and EBV. PLoS Pathogens 10 (3), e1004008.

Cohen, M.S., Chen, Y.Q., McCauley, M., et al., 2011. Prevention of HIV-1 infection with early antiretroviral therapy. The New England Journal of Medicine 365, 493–505.

Elkington, R., Shoukry, N., Walker, S., et al., 2004. Cross-reactive recognition of human and primate cytomegalovirus sequences by human CD4 cytotoxic T lymphocytes specific for glycoprotein B and H. European Journal of Immunology 34, 3216–3226.

Faria, N.R., Rambaut, A., Suchard, M.A., et al., 2014. The early spread and epidemic ignition of HIV-1 in human populations. Science 346 (6205), 56–61.

Flajnik, M.F., Kasahara, M., 2010. Origin and evolution of the adaptive immune system: genetic events and selective pressures. Nature Reviews Genetics 11 (1), 47–59.

Fromm, J., 2005. Types and Forms of Emergence. University Kassel, Germany.

Gallo, R.C., Sarin, P.S., Gelmann, E.P., et al., 1983. Isolation of human T-cell leukemia virus in acquired immune deficiency syndrome (AIDS). Science 220 (4599), 865–867.

Gellman, B., July 11, 2000. 'Washington Post': South African President Thabo Mbeki Trying to Highlight 'Grinding Poverty' in Context of AIDS Crisis.

Gilbert, M., Thomas, P., Rambaut, A., et al., 2007. The emergence of HIV/AIDS in the Americas and beyond. Proceedings of the National Academy of Sciences of the United States of America 104 (47), 18566–18570.

Gottlieb, M.S., 1981. Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. New England Journal of Medicine 305, 1425–1431.

Hertz, T., Nolan, D., James, I., et al., 2011. Mapping the landscape of host-pathogen coevolution: HLA class I binding and its relationship with evolutionary conservation in human and viral proteins. Journal of Virology 85 (3), 1310–1321.

Kawashima, Y., Pfafferott, K., Frater, J., et al., April 2, 2009. Adaptation of HIV-1 to human leukocyte antigen class I. Nature 458 (7238), 641–645.

Kaufman, J., 2010. The evolution of the adaptive immune system of jawed vertebrates. In: Kaufmann, S.H.E., Sacks, R.B. (Eds.), Immunology of Infectious Diseases. American Society for Microbiology Press, Washington.

Lalani, A.S., McFadden, G., 1999. Evasion and exploitation of chemokines by viruses. Cytokine & Growth Factor Reviews 10, 219–233.

Malouli, D., Hansen, S.G., Nakayasu, E.S., et al., May 2014. Journal of Clinical Investigation 124 (5), 1928–1944.

McGeoch, D.J., Rixon, F.J., Davison, A.J., 2006. Topics in herpesvirus genomics and evolution. Virus Research 117 (1), 90–104.

Moore, C.B., John, M., James, I.R., et al., 2002. Evidence of HIV-1 adaptation to HLA-restricted immune responses at a population level. Science 296 (5572), 1439–1443.

Payne, R., Muenchhoff, M., Mann, J., et al., 2014. Impact of HLA-driven HIV adaptation on virulence in populations of high HIV seroprevalence. PNAS 111 (50), E5393–E5400.

Price, D.A., Goulder, P.J.R., Klenerman, P., et al., 1997. Positive selection of HIV-1 cytotoxic T lymphocyte escape variants during primary infection. Proceedings of the National Academy of Sciences of the United States of America 94 (5), 1890–1895.

Shapira, Y., Agmon-Levin, N., Shoenfeld, Y., 2010. Defining and analyzing geoepidemiology and human autoimmunity. Journal of Autoimmunity 34 (3), J168–J177.

Venturi, V., Kedzierska, K., Price, D.A., et al., December 5, 2006. Sharing of T cell receptors in antigen-specific responses is driven by convergent recombination. Proceedings of the National Academy of Sciences of the United States of America 103 (49), 18691–18696. Epub 2006 Nov 27.

Virgin, H.W., Wherry, E.J., Ahmed, R., 2009. Redefining chronic viral infection. Cell 138 (1), 30–50.

Wertheim, J.O., Smith, M.D., Smith, D.M., et al., September 2014. Evolutionary origins of human herpes Simplex viruses 1 and 2. Molecular Biology and Evolution 31 (9), 2356–2364.

Worobey, M., Telfer, P., Souquière, S., et al., 2010. Island biogeography reveals the deep history of SIV. Science 329 (5998), 1487.

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ON HUMAN NATURE

BIOLOGY, PSYCHOLOGY, ETHICS, POLITICS, AND RELIGION

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On Human Nature: Biology, Psychology, Ethics, Politics, and Religion covers the present state of knowledge on human diversity and its adaptive significance through a broad and eclectic selection of representative chapters. This transdisciplinary work brings together specialists from various fields who rarely interact, including geneticists, evolutionists, physicians, ethologists, psychoanalysts, anthropologists, sociologists, theologians, historians, linguists, and philosophers.

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An imprint of Elsevier
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ISBN 978-0-12-420190-3