


# In the Light of Evolution: Volume IV: The Human Condition

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## Volume IV: The Human Condition

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JOHN C. AVISE and FRANCISCO J. AYALA, *Editors*

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*Cover image:* Commonly referred to as the "priest-king," this Harappan Civilization sculpture (ca. 2000–1900 B.C.) was recovered from the Indus Valley Mohenjo-daro archaeological site in Pakistan. The statue symbolizes the human condition as a representation of bodily form and function, and is an example of culture and the arts. Image copyright J. M. Kenoyer, courtesy of the Department of Archaeology and Museums, Government of Pakistan/Harappa.com.



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# Arthur M. Sackler, M.D.
# 1913–1987

Born in Brooklyn, New York, Arthur M. Sackler was educated in the arts, sciences, and humanities at New York University. These interests remained the focus of his life, as he became widely known as a scientist, art collector, and philanthropist, endowing institutions of learning and culture throughout the world.

He felt that his fundamental role was as a doctor, a vocation he decided upon at the age of four. After completing his internship and service as house physician at Lincoln Hospital in New York City, he became a resident in psychiatry at Creedmoor State Hospital. There, in the 1940s, he started research that resulted in more than 150 papers in neuroendocrinology, psychiatry, and experimental medicine. He considered his scientific research in the metabolic basis of schizophrenia his most significant contribution to science and served as editor of the *Journal of Clinical and Experimental Psychobiology* from 1950 to 1962. In 1960 he started publication of *Medical Tribune*, a weekly medical newspaper that reached over one million readers in 20 countries. He established the Laboratories for Therapeutic Research in 1938, a facility in New York for basic research that he directed until 1983.

As a generous benefactor to the causes of medicine and basic science, Arthur Sackler built and contributed to a wide range of scientific institutions: the Sackler School of Medicine established in 1972 at Tel Aviv University, Tel Aviv, Israel; the Sackler Institute of Graduate Biomedical Science at New York University, founded in 1980; the Arthur M. Sackler Science Center dedicated in 1985 at Clark University, Worcester, Massachusetts; and the Sackler School of Graduate Biomedical Sciences, established in 1980, and the Arthur M. Sackler Center for Health Communications, established in 1986, both at Tufts University, Boston, Massachusetts.

His pre-eminence in the art world is already legendary. According to his wife Jillian, one of his favorite relaxations was to visit museums and art galleries and pick out great pieces others had overlooked. His interest in art is reflected in his philanthropy; he endowed galleries at the Metropolitan Museum of Art and Princeton University, a museum at Harvard

University, and the Arthur M. Sackler Gallery of Asian Art in Washington, D.C. True to his oft-stated determination to create bridges between peoples, he offered to build a teaching museum in China, which Jillian made possible after his death, and in 1993 opened the Arthur M. Sackler Museum of Art and Archaeology at Peking University in Beijing.

In a world that often sees science and art as two separate cultures, Arthur Sackler saw them as inextricably related. In a speech given at the State University of New York at Stony Brook, *Some reflections on the arts, sciences and humanities*, a year before his death, he observed: "Communication is, for me, the *primum movens* of all culture. In the arts . . . I find the emotional component most moving. In science, it is the intellectual content. Both are deeply interlinked in the humanities." The Arthur M. Sackler Colloquia at the National Academy of Sciences pay tribute to this faith in communication as the prime mover of knowledge and culture.

# Contents

# Preface to the *In the Light of Evolution* Series

Biodiversity—the genetic variety of life—is an exuberant product of the evolutionary past, a vast human-supportive resource (aesthetic, intellectual, and material) of the present, and a rich legacy to cherish and preserve for the future. Two urgent challenges, and opportunities, for 21st-century science are to gain deeper insights into the evolutionary processes that foster biotic diversity, and to translate that understanding into workable solutions for the regional and global crises that biodiversity currently faces. A grasp of evolutionary principles and processes is important in other societal arenas as well, such as education, medicine, sociology, and other applied fields including agriculture, pharmacology, and biotechnology. The ramifications of evolutionary thought also extend into learned realms traditionally reserved for philosophy and religion.

In 1973, Theodosius Dobzhansky penned a short commentary entitled "Nothing in biology makes sense except in the light of evolution." Most scientists agree that evolution provides the unifying framework for interpreting biological phenomena that otherwise can often seem unrelated and perhaps unintelligible. Given the central position of evolutionary thought in biology, it is sadly ironic that evolutionary perspectives outside the sciences have often been neglected, misunderstood, or purposefully misrepresented.

The central goal of the *In the Light of Evolution* (*ILE*) series is to promote the evolutionary sciences through state-of-the-art colloquia—in the series of Arthur M. Sackler colloquia sponsored by the National Academy of Sciences—and their published proceedings. Each installment explores

evolutionary perspectives on a particular biological topic that is scientifically intriguing but also has special relevance to contemporary societal issues or challenges. Individually and collectively, the *ILE* series aims to interpret phenomena in various areas of biology through the lens of evolution, address some of the most intellectually engaging as well as pragmatically important societal issues of our times, and foster a greater appreciation of evolutionary biology as a consolidating foundation for the life sciences.

The organizers and founding editors of this effort (Avise and Ayala) are the academic grandson and son, respectively, of Theodosius Dobzhansky, to whose fond memory this *ILE* series is dedicated. May Dobzhansky's words and insights continue to inspire rational scientific inquiry into nature's marvelous operations.

John C. Avise and Francisco J. Ayala
Department of Ecology and Evolutionary Biology,
University of California, Irvine (January 2007)

# Preface to *In the Light of Evolution, Volume IV: The Human Condition*

The year 2009 marked the 200th anniversary of Charles Darwin's birth and the 150th anniversary of his most influential publication (Darwin, 1859). Darwin transformed the biological sciences in much the same way that Nicolaus Copernicus, Galileo Galilei, and Isaac Newton had transformed the physical sciences—by demonstrating that the universe operates according to natural laws that fall within the purview of rational scientific inquiry. In 1543, Copernicus published *De revolutionibus orbium celestium* ("On the Revolutions of the Celestial Spheres") which challenged conventional wisdom that the Earth was the center of Creation, and instead promoted the idea that natural laws govern the motion of physical objects in the universe. More than three centuries later, in *The Origin of Species*, Darwin developed the equally revolutionary concept that a natural but nonrandom process—natural selection—can yield biological adaptations that otherwise exude the superficial aura of direct craftsmanship by an intelligent agent.

This book is the outgrowth of the Arthur M. Sackler Colloquium "The Human Condition," which was sponsored by the National Academy of Sciences on December 11–12, 2009, at the Academy's Arnold and Mabel Beckman Center in Irvine, California. It is the fourth in a series of colloquia under the umbrella title "In the Light of Evolution." The first book in this series was titled *In the Light of Evolution, Volume I: Adaptation and Complex Design* (Avise and Ayala, 2007). The second was *In the Light of Evolution, Volume II: Biodiversity and Extinction* (Avise et al., 2008). The third book—*In the Light of Evolution, Volume III: Two Centuries of Darwin* (Avise and Ayala,

2009)—presented the proceedings of a Sackler Colloquium that kicked off the bicentennial celebration of Darwin's birth and the sesquicentennial of *The Origin of Species*. The current book registers the proceedings of a Sackler Symposium that was timed to help close the bicentennial celebration by addressing the modern Darwinian legacy as it relates to human evolution and the human condition. Thus, the papers in this collection are devoted to "anthropogeny" (Varki et al., 2008): understanding the evolutionary origins of humans and their biological and cultural traits.

Actually, Darwin barely mentioned *Homo sapiens* in the *Origin of Species*, coyly stating only that "much light will be thrown on the origin of man and his history." More than a decade later, however, Darwin addressed human evolution at considerable length in *The Descent of Man and Selection in Relation to Sex* (1871a) wherein can be found many thoughtful passages, such as, "Man may be excused for feeling some pride at having risen, though not through his own exertions, to the very summit of the organic scale; and the fact of his having thus risen, instead of having been aboriginally placed there, may give him hopes for a still higher destiny in the distant future." Of course, much has been learned about humanity's evolutionary origins and biological conditions since Darwin's time, not least from the evidence of paleontology, comparative vertebrate biology, and genomics. In the chapters of this book, leading evolutionary biologists and philosophers of science reflect upon and commemorate the Darwinian Revolution as it relates to the human condition at levels ranging from the molecular to the theological. Chapters in these proceedings are organized into three parts: (I) Human Phylogenetic History and the Paleontological Record, (II) Structure and Function of the Human Genome; and (III) Cultural Evolution and the Uniqueness of Being Human. The diverse topics addressed in these chapters give some indication of the vast breadth and depth of modern scientific research on Darwinian evolution of the human state.

# Part I

## HUMAN PHYLOGENETIC HISTORY AND THE PALEONTOLOGICAL RECORD

Precious few nonhuman fossils in humanity's recent "family tree" were known to science in the mid-1800s, but, interestingly, Darwin once briefly held in his hands one of these treasures: a Neandertal skull that had been excavated from Gibraltar in 1848. As additional hominid fossils of various geological ages gradually were unearthed in the ensuing decades (e.g., in Java, Africa, and Europe), anthropologists grappled with naming and classifying such remains and interpreting their proper places in prehuman evolutionary history. Such paleontological finds can be of two general types: fossilized body parts such as leg bones, the pelvic girdle, or the cranium (giving glimpses into humanity's anatomical heritage), and nonbiotic physical artifacts such as stone tools or cave paintings that can offer important clues about humanity's cultural heritage. A different but complementary approach to studying human origins has entailed evolutionary reconstructions based on morphological, molecular-genetic, or other features of modern *Homo sapiens* compared to those of other extant primates. In these reconstructions, phylogeneticists take advantage of the voluminous biological information currently on display in living organisms to deduce the evolutionary ages and properties of the ancestors that humans shared with various other primates, thereby in effect delving backward through time, indirectly.

In Chapter 1, Bernard Wood describes some of the special challenges that have confronted anthropologists wishing to reconstruct human evolution based on morphological evidence (both from fossils and extant primates). One fundamental limitation has been the relative paucity of

fossilized hominin material, but additional complications have come from shifting taxonomic paradigms and nomenclatural practices within the systematics community itself, as well as from continuing debates about phylogenetic methods and species concepts, especially as they apply to fossil material. The net result has been an oft-confusing proliferation of species names and taxonomic realignments for putative human ancestors. To help simplify this imbroglio, Wood compiles, describes, and provides geological dates for all named fossil taxa in the human clade, ranging from anatomically modern *Homo sapiens* back to various archaic hominins and "possible hominins" that lived several million years ago, and many taxa temporally in between. Wood also addresses several looming opportunities for the field of comparative primate morphology, such as the use of new imaging technologies that should help to clarify (by permitting more detailed levels of examination) when similar anatomical traits in different taxa register genuine homology (shared ancestry) versus homoplasy (evolutionary convergence from separate ancestors).

In Chapter 2, Juan Luis Arsuaga reviews the history of scientific debate, beginning in Darwin's era, about the precise phylogenetic interrelationships among modern humans and the various great apes of Africa and Asia. Another longstanding debate in anthropology is whether two or more species of more recent human ancestry ever inhabited the planet at the same time (which might seem unlikely based on general ecological considerations for competitive, large-brained primates). Traditionally, fossil-based assessments of this question relied heavily on rather meager population-level data from craniodental anatomy, but more comprehensive morphotypic descriptions are now becoming possible as the available number of known postcranial hominin fossils has swelled as well. Arsuaga reviews these recent fossil-based discoveries about anatomical variation within and among particular proto-human populations dating to more than 0.5 mya, and he concludes that the data are consistent with the more-or-less contemporaneous presence of either different species (depending on one's definition of species) or, perhaps, morphologically distinct populations within a single species that seems to have been much more polytypic in anatomy than are modern humans.

Increasingly in recent years, the field of physical anthropology has shifted much of its attention from morphology-based appraisals of human evolution to historical reconstructions based on molecular-genetic and genomics data. In Chapter 3, Morris Goodman and Kirsten Sterner review the history of molecular approaches in refining our understanding of primate phylogeny, for example, in revealing the branching orders of lineages that led to extant great apes and humans. They then argue that a modern "phylogenomic approach" can go well beyond phylogeny reconstruction *per se* by helping to identify Darwinian (positively selected) genetic

changes (in expression profiles as well as protein-coding sequences) that might mechanistically underlie the evolution of such distinctive human features as expanded cognitive ability, sociality, and language. The authors illustrate this phylogenomic approach by recent work that implicates particular loci in the adaptive evolution of high levels of aerobic energy metabolism that a large mammalian brain necessitates.

In Chapter 4, Angela Hancock and several other authors associated with the laboratory of Anna Di Rienzo extend this general phylogenomic perspective to analyze genome-wide scans of SNPs (single-nucleotide polymorphisms) in numerous human populations representing distinct ecoregions on planet Earth, or that differ in fundamental subsistence mode with respect to diet. In principle, genetic variation among geographic populations might register adaptive differences promoted by environmental selection, or historical population-demographic effects that are mostly independent of the ecological selective regime *per se*. Hancock and her coauthors attempt to distinguish these two classes of historical causation by searching for consistent distributions of SNPs vis-à-vis human diet and ecoregion, after applying analytical methods designed to control for gene-environment associations that might be due to historical population demography. The authors conclude that strong signals of natural selection related to diet and climate exist for SNPs at particular genes that are centrally involved in carbohydrate utilization and energy metabolism. The authors also compare their phylogenomic approach and findings to those of previous genome-wide association studies in humans.

Africa is humanity's evolutionary cradle, and its contemporary populations retain extraordinary genetic and linguistic diversity that offers anthropologists a wellspring of biological and cultural information about human history on that continent over the past 200 millennia. For example, with respect to languages, researchers recognize more than 2,000 ethnolinguistic groups that can be classified into four major African language families; and with respect to genetic lineages, mitochondrial (mt) DNA (which is inherited maternally) and the Y chromosome (which is transmitted paternally) both display higher genealogical diversity and evolutionary depth in Africa than in many other regions of the planet combined (as might be expected under a model of African ancestry for all modern humans). In Chapter 5, Laura Scheinfeldt, Sameer Soi, and Sarah Tishkoff address the demographic history of human populations in Africa by compiling and comparing scientific information from archaeology (including cultural artifacts), comparative linguistics, and molecular genetics. Their synthesis reveals various signatures of past population movements on the continent, sometimes registered in particular genetic markers (either neutral or under selection), sometimes registered in cultural practices (such as agriculture and pastoralism), sometimes relatable to geophysical changes

in the environment, and sometimes reflected to varied degrees in the current spatial distributions of languages. The net result is a fascinating but complex picture of African human demographic history, presented in a broad framework that can be further tested as additional archaeological, linguistic, and genetic analyses (especially from autosomal loci) eventually are incorporated into the synthesis.

# 1

# Reconstructing Human Evolution: Achievements, Challenges, and Opportunities

BERNARD WOOD

This contribution reviews the evidence that has resolved the branching structure of the higher primate part of the tree of life and the substantial body of fossil evidence for human evolution. It considers some of the problems faced by those who try to interpret the taxonomy and systematics of the human fossil record. How do you to tell an early human taxon from one in a closely related clade? How do you determine the number of taxa represented in the human clade? How can homoplasy be recognized and factored into attempts to recover phylogeny?

This contribution begins by considering two achievements relevant to reconstructing human evolution: resolving the branching structure of the higher primate part of the tree of life and the recovery of a substantial body of fossil evidence for human evolution (Fig. 1.1). The second part considers some of the challenges faced by those who try to interpret the taxonomy and systematics of the human fossil record. How do you to tell an early human taxon from one in a closely related clade? How many taxa are represented in the human clade? How to recognize and cope with homoplasy in and around the human clade? The third part of this contribution suggests how new ways of gathering morphological data may help researchers overcome some of the challenges referred to above.

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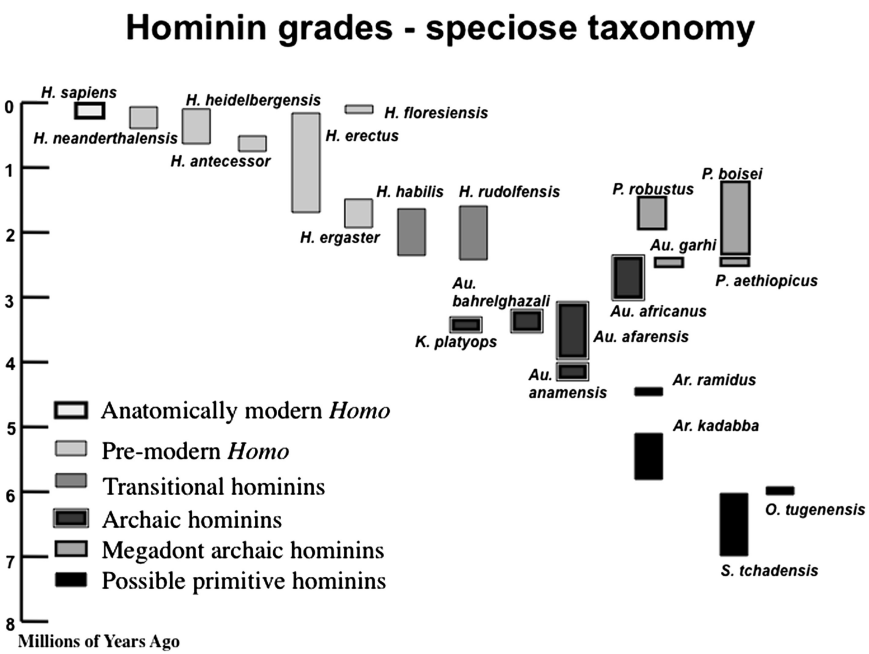


FIGURE 1.1 Taxa recognized in a typical speciose hominin taxonomy. Note that the height of the columns reflects either uncertainties about the temporal age of a taxon, or in cases where there are well-dated horizons at several sites, it reflects current evidence about the earliest (called the first appearance datum, or FAD) and the most recent (called the last appearance datum, or LAD) fossil evidence of any particular hominin taxon. However, the time between the FAD and the LAD is likely to represent the minimum time span of a taxon, because it is highly unlikely that the fossil record of a taxon, and particularly the relatively sparse fossil records of early hominin taxa, include the earliest and most recent fossil evidence of a taxon. The newest archaic hominin taxon, the *ca.* 1.9 Ma *Australopithecus sediba,* would occupy the space just above the box for *Au. africanus.*

## ACHIEVEMENTS

### Resolving the Branching Structure of the Higher Primate Part of the Tree of Life

The first systematic investigation of the relationships among the living great ape taxa was in 1863 by Thomas Henry Huxley. In the second of the three essays in his *Evidence as to Man's Place in Nature,* Huxley addresses "the place which Man occupies in nature and of his relations to the universe of things" (1863, p. 57). After reviewing the evidence Huxley

concluded that "the structural differences which separate Man from the Gorilla and the Chimpanzee are not so great as those which separate the Gorilla from the lower apes" (p. 103). The next significant advance in our understanding of the relationships among the great apes came when developments in biochemistry and immunology made in the first half of the 20th century allowed the focus of the search for evidence to be expanded beyond traditional gross morphological evidence to the properties of molecules (Goodman, 1963a; Zuckerkandl, 1963; Sarich and Wilson, 1967a), to the structure of proteins (King and Wilson, 1975), and most recently to the composition of the genome (Ruvolo, 1997; Bradley, 2008). A recent molecular supermatrix analysis based on 15 mitochondrial and 43 nuclear genes (Fabre et al., 2009) provides strong support for modern humans being more closely related to chimpanzees and bonobos than to any other living great ape. Gorillas are more distantly related to modern humans than to chimpanzees and bonobos, and a recent report notwithstanding (Grehan and Schwartz, 2009), the orangutan is the great ape most distantly related to modern humans; these relationships can also be expressed in the form [*Pongo* (*Gorilla* (*Pan, Homo*))]. This recent molecular supermatrix analysis effectively removes any reasonable doubt that extant *Pan* species are more closely related to modern humans than they are to extant *Gorilla* taxa. This is an important advance in our understanding of human evolution because, in combination with the principle of parsimony, it enables researchers to generate hypotheses about character evolution within the great ape clade. These hypotheses can then be used as the equivalent of a null hypothesis when considering where to place newly discovered fossil great ape taxa.

**The Human Fossil Record**

The fossil record of the human clade consists of fossil evidence for modern humans plus that of all extinct taxa that are hypothesized to be more closely related to modern humans than to any other living taxon. Not so long ago nearly all researchers were comfortable with according the human clade the status of a family, the Hominidae, with the nonhuman extant great apes (i.e., chimpanzees, bonobos, gorillas, and orangutans) placed in a separate family, the Pongidae. But given the abundant evidence for a closer relationship between *Pan* and *Homo* than between *Pan* and *Gorilla* (see above), many researchers have concluded that the human clade should be distinguished beneath the level of the family in the Linnaean hierarchy. These researchers now use the family Hominidae for *all* of the extant great apes (including modern humans), and they use the subfamily Homininae either for *Gorilla, Pan,* and *Homo* [e.g., Harrison (2010)] or for just *Pan* and *Homo.* Some of the researchers

who opt for the former, more inclusive, solution use the tribe Hominini for both the chimpanzee/bonobo and the human clades and treat the human clade as a subtribe, the Hominina (so individuals and taxa within it are referred to as "homininans"). Other researchers use the tribe Hominini to refer to just the human clade. Thus, in this scheme the taxa within the human clade are referred to as "hominin" taxa, and the individual fossils in those taxa are called "hominin" fossils. In the first, more inclusive, scheme, taxa in the chimpanzee/bonobo clade are referred to as "paninans," whereas in the second scheme they are referred to as "panins." In this review we use the second scheme and its "hominin/panin" terminology.

## Classifying Hominins

Whereas clades reflect the *process* of evolutionary history, the grade concept (Huxley, 1958) is based on assessing the *outcome* of evolutionary history. Taxa in the same grade eat the same sorts of foods and share the same posture and mode(s) of locomotion; no store is set by how they came by those behaviors. The judgment about how different two diets or two locomotor strategies have to be before the taxa concerned are considered to belong to different grades is still a subjective one, but until we can be sure we are generating reliable hypotheses about the relationships among hominin taxa the grade concept helps sort taxa into broad functional categories, albeit sometimes frustratingly "fuzzy" (e.g., where to place *Homo floresiensis*) ones. The grades used in this review are "Anatomically modern *Homo*," "Premodern *Homo*," "Transitional hominins," "Archaic hominins," "Megadont archaic hominins," and "Possible hominins." We use a relatively speciose taxonomic hypothesis (Table 1.1) and present the species within each grade in the historical order the taxa were recognized, not in their temporal order.

## Discovering Fossil Hominins

The earliest discoveries of fossil hominins were chance events at isolated sites. The circumstances of the first hominin fossil to be discovered, at Goat's Hole Cave in Paviland on the Gower Peninsula in South Wales, was typical. Local people interested in natural history were exploring coastal caves when they found animal fossils and later a burial of a fossil hominin. In some cases individuals have taken advantage of what otherwise were not auspicious circumstances to look for fossils. Captain Brome was an ardent fossil collector, so when he was posted to the Rock of Gibraltar as the Governor of the Military Prison he thought it more sensible to put the prisoners to work excavating rather than just break-

TABLE 1.1 Hominin Species in a Speciose Taxonomy Sorted into Six Grade Groupings

| Grade | Species Included in a Splitting Taxonomy |
|---|---|
| Possible hominins | *Ar. ramidus*[a] |
| | *O. tugenensis* |
| | *S. tchadensis* |
| | *Ar. kadabba* |
| Archaic hominins | *Au. africanus*[a] |
| | *Au. afarensis*[a] |
| | *Au. bahrelgazali* |
| | *Au. anamensis* |
| | *Au. garhi* |
| | *K. platyops* |
| | *Au. sediba* |
| Megadont archaic hominins | *P. robustus*[a] |
| | *P. boisei* |
| | *P. aethiopicus* |
| Transitional hominins | *H. habilis*[a] |
| | *H. rudolfensis* |
| Premodern *Homo* | *H. erectus*[a] |
| | *H. neanderthalensis* |
| | *H. heidelbergensis* |
| | *H. ergaster* |
| | *H. antecessor* |
| | *H. floresiensis* |
| Anatomically modern *Homo* | *H. sapiens*[a] |

[a]A lumping taxonomy might only recognize these species.

ing rocks, and it was during excavations at Forbe's Quarry using the labor of military prisoners that the Gibraltar Neanderthal cranium was recovered. Its discovery was announced at a meeting of the Gibraltar Scientific Society in 1848, and the records of scientific and natural history societies (e.g., the East Africa and Uganda Natural History Society) have proved to be a rich source of information about possible hominin fossil sites.

The first researcher to deliberately travel to another continent in search of hominin fossils was Eugène Dubois. Dubois' interest in human evolution came from reading Charles Darwin and especially Ernst Haeckel, who was convinced that our ancestors had emerged in the jungles of Asia. The discovery of primate fossils in the Siwalik Hills of India by Theobald in 1878 (and their description by Lydekker in 1879) encouraged Dubois' conviction that the creatures Haeckel had referred to as the *Pithecanthropi* in the *History of Creation* might be found in the Dutch East Indies. After resigning his university post in 1887 Dubois enlisted as a medical officer in the Royal Dutch East Indies Army and

began his search for the evolutionary link between apes and modern humans. He found a piece of hominin lower jaw at Kedung Brubus, Java, in November 1890, and in 1891 Dubois began excavating along the banks of the Solo River near the village of Trinil. In September of that year a hominin molar was discovered, and in October Dubois' team of excavators found the hominin skullcap that was to become the type specimen of *Pithecanthropus erectus,* later designated as *Homo erectus.*

The first important hominin fossil discoveries in Africa, the cranium found at Broken Hill (now Kabwe) in 1921 and the Taung child's skull recovered in 1924, were both chance discoveries, and it took more than 50 years for the search for hominin sites in Africa to become more systematic. In the late 1980s the Paleoanthropological Inventory of Ethiopia (Asfaw et al., 1990) successfully located potential hominin fossil sites on a regional scale. Led by Berhane Asfaw, the inventory used Landsat thematic mapping (TM) and large-format camera high-resolution images. The former measures the intensity of reflected sunlight in seven wavebands, and the resulting color images were used to identify the distinctive ash layers, or tephra, that are typically found in the types of strata that contain Plio-Pleistocene fossils. The two sets of data were used to identify promising sedimentary basins, which were explored by vehicle and on foot to verify the presence of potential sites. At least two sources of hominin fossils in the Ethiopian Rift Valley, the site complex within the Kesem-Kebena basin in the north and the site of Fejej in the south, were located this way.

### Anatomically Modern *Homo*

This grade includes hominin fossil evidence that is indistinguishable from the morphology found in at least one regional population of modern humans. Modern humans belong to the species *Homo sapiens* Linnaeus 1758, and the earliest *H. sapiens* fossils are dated to just less than 200 ka. Since the initial discovery of a fossil modern human in 1822–1823 in Goat's Hole Cave in Wales, fossil evidence of *H. sapiens* has been recovered from sites on all continents except Antarctica. Many *H. sapiens* fossils are burials, so the fossil evidence is abundant and generally in good condition. The earliest evidence of anatomically modern human morphology in the fossil record comes from Omo Kibish in Ethiopia (McDougall et al., 2005), and it is also in Africa that we find evidence of crania that are generally more robust and archaic-looking than those of anatomically modern humans, yet they are not archaic or derived enough to justify being allocated to *Homo heidelbergensis* or to *Homo neanderthalensis* (see below). Specimens in this category include Jebel Irhoud from North Africa, Laetoli 18 from East Africa, and Florisbad and the

Cave of Hearths from southern Africa. There is undoubtedly a gradation in morphology that makes it difficult to set the boundary between anatomically modern humans and *H. heidelbergensis,* but the variation in the later *Homo* fossil record is too great to be accommodated in a single taxon. Researchers who wish to make a distinction between fossils such as Florisbad and Laetoli 18 and subrecent and living modern humans either do so taxonomically by referring the former specimens to a separate species, *Homo helmei* Dreyer 1935, or they distinguish them informally as "archaic *Homo sapiens.*"

**Premodern *Homo***

This grade grouping includes Pleistocene *Homo* taxa that lack the derived and distinctive size and shape of the modern human cranium and postcranial skeleton. Some individuals in these taxa possessed only medium-sized brains, yet they exhibit modern human-like body proportions. The first fossil taxon to be recognized in this grade is *H. neanderthalensis* King 1864, whose temporal range is *ca.* 200–28 ka (but if the Sima de los Huesos material is included, then it is *ca.* >450–28 ka). The first example of *H. neanderthalensis* to be discovered was a child's cranium recovered in 1829 from a cave in Belgium called Engis, but the type specimen, the Neanderthal 1 skeleton, was found in 1856 at the Kleine Feldhofer Grotte in Elberfield, Germany. Fossil evidence for *H. neanderthalensis* has since been found in Europe as well as in the Near East, the Levant, and western Asia. The distinctive features of the cranium of *H. neanderthalensis* include thick, double-arched brow ridges, a face that projects anteriorly in the midline, a large nose, laterally projecting and rounded parietal bones, and a rounded, posteriorly projecting occipital bone.

Mandibular and dental features include a retromolar space, distinctively high incidences of some nonmetrical dental traits, and thinner tooth enamel than in modern humans. The average endocranial volume of *H. neanderthalensis* was the same as that of contemporary *H. sapiens,* but it is larger than that of living modern humans. Postcranially, *H. neanderthalensis* individuals were stout with a broad rib cage, a long clavicle, a wide pelvis, and limb bones that are generally robust with well-developed muscle insertions. The distal extremities tend to be short compared with most modern *H. sapiens,* but *H. neanderthalensis* was evidently an obligate biped. The generally well-marked muscle attachments and the relative thickness of long bone shafts point to a strenuous lifestyle. For some researchers the *H. neanderthalensis* hypodigm is restricted to fossils from Europe and the Near East that used to be referred to as "Classic" Neanderthals. Others interpret the taxon more inclusively and include fossil evidence that is generally older and less distinctive (e.g., Steinheim,

Swanscombe, and from the Sima de los Huesos). The first DNA recovered from a fossil hominin was from the type specimen of *H. neanderthalensis* (Krings et al., 1997), and recently Green et al. (2008) sequenced the complete mtDNA of a specimen from Vindija. Briggs et al. (2009) reported the mtDNA sequences of five individuals and concluded that genetic diversity within *H. neanderthalensis* was substantially lower than that in modern humans.

The next fossil hominin taxon in this grade to be discovered was *H. erectus* (Dubois 1893) Weidenreich 1940. Its temporal range is *ca.* 1.8 Ma to *ca.* 30 ka. The initial discovery at Kedung Brubus was made in 1890, but the type specimen was recovered in 1891 from Trinil. *H. erectus* is known from sites in Indonesia (e.g., Trinil, Sangiran, and Sambungmachan), China (e.g., Zhoukoudian and Lantian), and Africa (e.g., Olduvai Gorge and Melka Kunturé). The hypodigm of *H. erectus* is dominated by cranial remains; there is some postcranial evidence but very few hand and foot fossils. Crania belonging to *H. erectus* have a low vault, a substantial more-or-less continuous torus above the orbits, and a sharply angulated occipital region, and the inner and outer tables of the cranial vault are thick. The body of the mandible is more robust than that of *H. sapiens,* it lacks a chin, and the mandibular tooth crowns are generally larger and the premolar roots more complicated than those of modern humans. The limb proportions of *H. erectus* are modern human-like, but the shafts of the long bones are robust and those of the lower limb are flattened (the femur from front to back and the tibia from side to side) relative to those of modern humans. Overall, the cortical bone of *H. erectus* is thicker than is the case in modern humans. All of the dental and cranial evidence points to a modern human-like diet for *H. erectus,* and the postcranial elements are consistent with an upright posture and obligate bipedalism.

The next taxon recognized within the genus *Homo* was *H. heidelbergensis* Schoetensack 1908. The initial discovery and the type specimen, the Mauer 1 adult mandible, was found in 1907 in a sand quarry near Heidelberg, Germany. Other evidence included in the taxon comes from sites in Europe (e.g., Petralona), the Near East (e.g., Zuttiyeh), Africa (e.g., Kabwe and Bodo), China (e.g., Dali, Jinniushan, Xujiayao, and Yunxian), possibly India (Hathnora), and depending on how inclusively *H. neanderthalensis* is interpreted, from the Sima de los Huesos at Atapuerca, Spain. The temporal range of *H. heidelbergensis* is *ca.* 600–100 ka. What sets this material apart from *H. sapiens* and *H. neanderthalensis* is the morphology of the cranium and the robusticity of the postcranial skeleton. Some *H. heidelbergensis* have endocranial volumes as large as those of some modern humans, but they are always more robustly built, with a thickened occipital region and a projecting face and with large separate ridges

above the orbits. Compared with *H. erectus* the parietals are expanded, the occipital is more rounded, and the frontal bone is broader. *H. heidelbergensis* is the earliest hominin to have a brain as large as that of some anatomically modern *Homo,* and its postcranial skeleton suggests that its robust long bones and large lower limb joints were well suited to long-distance travel. Researchers who see the African part of this hypodigm as distinctive refer it to a separate species, *Homo rhodesiensis.* Those who see the European component of the *H. heidelbergensis* hypodigm (e.g., Sima de los Huesos) as already showing signs of *H. neanderthalensis* autapomorphies would sink it into the latter taxon.

Those who support *Homo ergaster* Groves and Mazák 1975 as a separate species point to features that are more primitive than *H. erectus* (e.g., mandibular premolar root and crown morphology) and those that are less derived than *H. erectus* (e.g., vault and cranial base morphology) (Wood, 1991). However, many researchers are unconvinced there are sufficient consistent differences between the hypodigms of *H. ergaster* and *H. erectus* (Spoor et al., 2007) to justify the former being a separate species. The taxon *Homo antecessor* Bermúdez de Castro et al. 1997 was introduced for hominins recovered from the Gran Dolina site at Atapuerca, Spain. The researchers who found the remains claim the combination of a modern human-like facial morphology with large and relatively primitive tooth crowns and roots is not seen in *H. heidelbergensis* (see below), and they see *H. antecessor* and not *H. heidelbergensis* as the likely recent common ancestor of *H. neanderthalensis* and *H. sapiens.*

The most recent taxon to be added to the genus *Homo* is *H. floresiensis* Brown et al. 2004. It is only known from Liang Bua, a cave in Flores, and its temporal range is *ca.* 74–17 ka. The initial discovery and type specimen is LB1, an associated partial adult skeleton, but a second associated skeleton and close to 100 separate fossils representing up to 10 individuals have subsequently been recovered. This hominin displays a unique combination of early *Homo*-like cranial and dental morphology, a hitherto unknown suite of pelvic and femoral features, a small brain *(ca.* 417 $cm^3$), a small body mass (25–30 kg), and small stature (1 m). When it was first described researchers interpreted it as an *H. erectus,* or *H. erectus*-like, taxon that had undergone endemic dwarfing, but more recently researchers have suggested it could be a dwarfed *Homo habilis*-like transitional grade taxon (Brown and Moeda, 2009; Morwood and Jungers, 2009).

**Transitional Hominins**

For the purposes of this review, *H. habilis* and *Homo rudolfensis* are retained within *Homo,* but they are treated separately from the premod-

ern *Homo* grade (Wood and Collard, 1999). The taxon *H. habilis* Leakey, Tobias, and Napier 1964 was introduced for fossils recovered from Olduvai Gorge, Tanzania. The rest of the *H. habilis* hypodigm consists of other fossils found at Olduvai Gorge and of fossils from Ethiopia (Omo Shungura and Hadar) and Kenya (Koobi Fora and perhaps Chemeron). Some have claimed that there is also evidence of *H. habilis* in southern Africa at Sterkfontein, Swartkrans, and Drimolen. The *H. habilis* hypodigm consists of mostly cranial and dental evidence; only a few postcranial bones can be confidently assigned to that taxon (see below). The endocranial volume of *H. habilis* ranges from *ca.* 500 $cm^3$ to *ca.* 700 $cm^3$, but most commentators opt for an upper limit closer to 600 $cm^3$. All of the crania are wider at the base than across the vault, but the face is broadest in its upper part. The only postcranial fossils that can be assigned to *H. habilis* with confidence are the postcranial bones associated with the type specimen, OH 7, and the associated skeleton, OH 62; isolated postcranial bones from Olduvai Gorge assigned to *H. habilis* (e.g., OH 10) could also belong to *P. boisei* (see below). If OH 62 is representative of *H. habilis* the skeletal evidence suggests that its limb proportions and locomotion (Ruff, 2009b) and carpal bones (Tocheri et al., 2007) were archaic hominin-like, and the curvature and well-developed muscle markings on the phalanges of OH 7 indicate that *H. habilis* was capable of powerful grasping. The inference that *H. habilis* used spoken language was based on links between endocranial morphology and language comprehension and production that are no longer supported by comparative evidence.

Some researchers suggest the transitional hominin grade contains a second taxon, *H. rudolfensis* (Alexeev 1986) *sensu* Wood 1992 (Wood, 1991), but not all researchers are convinced the scale and nature of the variation within early *Homo* justifies the recognition of two taxa (Tobias, 1991; Suwa et al., 1996). Its temporal range would be *ca.* 2.4–1.6 Ma, and aside from the lectotype KNM-ER1470 from Koobi Fora, Kenya, the members of the proposed hypodigm include other fossils recovered from Koobi Fora and those from Chemeron, Kenya, and Uraha, Malawi. Compared with *H. habilis* the absolute size of the brain case in *H rudolfensis* is greater, and its face is widest in its midpart whereas the face of *H. habilis* is widest superiorly. Despite the absolute size of the *H. rudolfensis* brain *(ca.* 725 $cm^3$), when it is related to estimates of body mass based on orbit size the brain is not substantially larger than those of the archaic hominins. The distinctive face of *H. rudolfensis* is combined with a robust mandibular corpus and mandibular postcanine teeth with larger, broader crowns and more complex premolar root systems than those of *H. habilis.* At present, no postcranial remains can be reliably linked with *H. rudolfensis.* The size of the mandible and postcanine teeth suggests that its diet made similar mechanical demands as those of the archaic hominins (see below).

**Archaic Hominins**

This grade includes all of the remaining unambiguously hominin taxa not conventionally included *in Homo* and *Paranthropus* (see below). The first taxon to be recognized in this grade was *Australopithecus africanus* Dart 1925. The type specimen, Taung 1, a juvenile skull with a partial natural endocast, was recovered in 1924 from the limeworks at Taung (formerly Taungs), now in South Africa. Most of the other fossil evidence for *Au. africanus* comes from two caves, Sterkfontein and Makapansgat, with other evidence coming from the Gladysvale cave. Unless the associated skeleton StW 573 from Mb 2 (Clarke, 2008) and 12 hominin fossils recovered from the Jacovec Cavern (Partridge et al., 2003) expands it, the temporal range of *Au. africanus* is *ca.* 3–2.4 Ma. The cranium, mandible, and the dentition are well sampled; the postcranial skeleton, and particularly the axial skeleton, is less well represented, but there is at least one specimen of each of the long bones, but many of the fossils have been crushed and deformed by rocks falling on the bones before they were fully fossilized. The picture that has emerged from morphological and functional analyses suggests that although *Au. africanus* was capable of walking bipedally it was probably more arboreally adapted (i.e., it was a facultative and not an obligate biped) than other archaic hominin taxa, such as *Australopithecus afarensis.* It had relatively large chewing teeth, and apart from the reduced canines the skull is relatively ape-like. Its mean endocranial volume is *ca.* 460 $cm^3$. 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.*

The taxon *Au. afarensis* Johanson, White, and Coppens 1978 is only known from East African sites. The type specimen is an adult mandible, LH 4, recovered in 1974 from Laetoli, Tanzania. The largest contribution to the *Au. afarensis* hypodigm comes from Hadar, but other sites in Ethiopia (Belohdelie, Brown Sands, Dikika, Fejej, Maka, and White Sands) and sites in Kenya (Allia Bay, Koobi Fora, and West Turkana) have contributed to it. The temporal range of *Au. afarensis* is *ca.* 3.7–3 Ma *(ca.* 4–3 Ma if the presence of *Au. afarensis* is confirmed at Belohdelie and Fejej). The *Au. afarensis* hypodigm includes a well-preserved skull, partial and fragmented crania, many lower jaws, sufficient limb bones to be able to estimate stature and body mass (Kimbel and Delezene, 2009), and a specimen, A.L.-288, that preserves *ca.* 25% of the skeleton of an adult female. Most body mass estimates range from *ca.* 30–45 kg, and the endocranial volume of *Au. afarensis* is estimated to be between 400 and 550 $cm^3$. It has smaller incisors than those of extant chimps/bonobos, but its premolars and molars are relatively larger. Comparative evidence suggests that the hind limbs of A.L.-288 are substantially shorter than those of a modern human of similar stature. The appearance of the

pelvis and the relatively short lower limb suggests that although *Au. afarensis* was capable of bipedal walking it was not adapted for long-range bipedalism. This indirect evidence for the locomotion of *Au. afarensis* is complemented by the discovery at Laetoli of several trails of fossil footprints. These provide very graphic direct evidence that at least one contemporary hominin, presumably *Au. afarensis,* but possibly *Kenyanthropus platyops* (see below), was capable of bipedal locomotion, but the Laetoli prints are less modern human-like than the 1.5-Ma footprints from Koobi Fora presumed to be of pre-modern *Homo* (Bennett, 2009). The upper limb, especially the hand (Tocheri et al., 2007) and the shoulder girdle, of *Au. afarensis* retains morphology that most likely reflects a significant element of arboreal locomotion. Although a recent study argues that sexual dimorphism in this taxon is relatively poorly developed, most researchers interpret it as showing substantial sexual dimorphism [e.g., Kimbel and Delezene (2009)].

The taxon *Australopithecus anamensis* Leakey, Feibel, McDougall, and Walker 1995 is also presently restricted to East Africa. The type specimen, KNM-KP 29281, was recovered in 1994 from Kanapoi, Kenya. Other sites contributing to the hypodigm are Allia Bay, also in Kenya, and the Middle Awash study area, Ethiopia. The temporal range of *Au. anamensis* is *ca.* 4.2–3.9 Ma. The fossil evidence consists of jaws, teeth, and postcranial elements from the upper and lower limbs. Most of the differences between *Au. anamensis* and *Au. afarensis* relate to details of the dentition. In some respects the teeth of *Au. anamensis* are more primitive than those *of Au. afarensis* (e.g., the asymmetry of the premolar crowns and the relatively simple crowns of the deciduous first mandibular molars), but in others (e.g., the low cross-sectional profiles and bulging sides of the molar crowns) they show some similarities to *Paranthropus* (see below). The upper limb remains are similar to those of *Au. afarensis,* and a tibia attributed to *Au. anamensis* has features associated with bipedality. Researchers familiar with the fossil evidence have suggested that *Au. anamensis* and *Au. afarensis* are most likely time successive taxa within a single lineage (Kimbel et al., 2006), with the Laetoli hypodigm of the former taxon intermediate between *Au. anamensis* and the Hadar hypodigm of *Au. afarensis.* The taxon *Australopithecus bahrelghazali* Brunet et al. 1996 is most likely a regional variant of *Au. afarensis* (Kimbel and Delezene, 2009). But the Chad discovery substantially extended the geographic range of early hominins and reminds us that important events in human evolution (e.g., speciation, extinction) may have been taking place well away from the very small (relative to the size of the African continent) regions sampled by the existing early hominin sites.

The most recently recognized taxon in this grade is *Kenyanthropus platyops* Leakey et al. 2001. The type specimen, KNM-WT 40000, a *ca.*

3.5–3.3-Ma relatively complete but distorted cranium, was found in 1999 at Lomekwi, West Turkana, Kenya. The main reasons Leakey et al. (2001) did not assign this material to *Au. afarensis* are its reduced subnasal prognathism, anteriorly situated zygomatic root, flat and vertically orientated malar region, relatively small but thick-enameled molars, and the unusually small $M^1$ compared with the size of the $P^4$ and $M^3$. Despite this unique combination of facial and dental morphology, White (2003) claims the new taxon is not justified because the cranium could be a distorted *Au. afarensis* cranium, but this explanation is not consistent with the small size of the postcanine teeth.

**Megadont Archaic Hominins**

This grade includes hominin taxa conventionally included in the genus *Paranthropus* and one *Australopithecus* species, *Australopithecus garhi.* The genus *Paranthropus,* into which *Zinjanthropus* and *Paraustralopithecus* are subsumed, was reintroduced when cladistic analyses suggested that the first three species discussed in this section most likely formed a clade. The term megadontia refers to both the absolute size of the postcanine teeth, as well as their relative size when compared with the length of the anterior tooth row.

The taxon *Paranthropus robustus* Broom 1938 was established to accommodate TM 1517, an associated skeleton recovered in 1938 from the southern African site of Kromdraai B. Other sites that contribute to the *P. robustus* hypodigm are Swartkrans, Gondolin, Drimolen, and Cooper's caves, all situated in the Blauuwbank Valley near Johannesburg, South Africa. The dentition is well represented in the hypodigm of *P. robustus,* but although some of the cranial remains are well preserved, most are crushed or distorted and the postcranial skeleton is not well represented. Research at Drimolen was only initiated in 1992 yet already more than 80 hominin specimens (many of them otherwise rare juvenile specimens) have been recovered and it promises to be a rich source of evidence about *P. robustus.* The temporal range of the taxon is *ca.* 2.0–1.5 Ma. The brain, face, and chewing teeth of *P. robustus* are on average larger than those of *Au. africanus,* yet the incisor teeth are smaller. The morphology of the pelvis and the hip joint is much like that of *Au. africanus; Paranthropus robustus* was most likely capable of bipedal walking, but it was probably not an obligate biped. It has been suggested that the thumb of *P. robustus* would have been capable of the type of grip necessary for the manufacture of simple stone tools, but this claim has not been accepted by all researchers. A second southern African taxon, *Paranthropus crassidens,* was proposed for the part of the

*P. robustus* hypodigm that comes from Swartkrans, but almost all researchers consider that taxon to be a junior synonym of *P. robustus.*

In 1959 Louis Leakey suggested that a new genus and species, *Zinjanthropus boisei* Leakey 1959, was needed to accommodate OH 5, a subadult cranium recovered in 1959 from Bed I, Olduvai Gorge, Tanzania. A year later John Robinson suggested that *Z. boisei* be subsumed into the genus *Paranthropus* as *Paranthropus boisei,* and in 1967 Phillip Tobias suggested it should be subsumed into *Australopithecus,* as *Australopithecus boisei;* in this review it is referred to as *Paranthropus boisei* (Leakey 1959) Robinson 1960. Additional fossils from Olduvai Gorge have subsequently been added to the hypodigm, as well as fossil evidence from the East African sites of Peninj, Omo Shungura, Konso, Koobi Fora, Chesowanja, and West Turkana. The temporal range of the taxon is *ca.* 2.3–1.4 Ma. *P. boisei* has a comprehensive craniodental fossil record, comprising several skulls and well-preserved crania, many mandibles, and isolated teeth. There is evidence of both large- and small-bodied individuals, and the range of the size difference suggests a substantial degree of body size sexual dimorphism despite its modest canine sexual dimorphism. *P. boisei* is the only hominin to combine a wide, flat face, massive premolars and molars, small anterior teeth, and a modest endocranial volume (*ca.* 480 $cm^3$). The face of *P. boisei* is larger and wider than that of *P. robustus,* yet their brain volumes are similar. The mandible of *P. boisei* has a larger and wider body or corpus than any other hominin (see *Paranthropus aethiopicus* below) and the tooth crowns apparently grow at a faster rate than has been recorded for any other early hominin. There is no postcranial evidence that can with certainty be attributed to *P. boisei* (Wood and Constantino, 2009), but some of the postcranial fossils from Bed I at Olduvai Gorge currently attributed to *H. habilis* may belong to *P. boisei.* The fossil record of *P. boisei* extends across approximately 1 million years, during which there is little evidence of any substantial change in the size or shape of the components of the cranium, mandible, and dentition (Wood et al., 1994).

The taxon *Paranthropus aethiopicus* (Arambourg and Coppens, 1968) Chamberlain and Wood 1985 was introduced as *Paraustralopithecus aethiopicus* to accommodate Omo 18.18 (or 18.1967.18), an edentulous adult mandible recovered in 1967 from Omo Shungura in Ethiopia. Other contributions to the hypodigm of this taxon have come from West Turkana and Kenya and probably also from Melema, Malawi, and Laetoli, Tanzania. The hypodigm is small, but it includes a well-preserved adult cranium from West Turkana (KNM-WT 17000) together with mandibles (e.g., KNM-WT 16005) and isolated teeth from Omo Shungura (some also assign the Omo 338y-6 cranium to this taxon). No published postcranial fossils have been assigned to *P. aethiopicus,* but a proximal tibia from Laetoli may belong to *P. aethiopicus.* The temporal range of

*P. aethiopicus* is *ca.* 2.5–2.3 Ma. *P. aethiopicus* is similar to *P. boisei* (see above) except that the face is more prognathic, the cranial base is less flexed, the incisors are larger, and the postcanine teeth are not so large or morphologically specialized.

The most recent addition to the megadont archaic hominin hypodigm is *Australopithecus garhi* Asfaw et al. 1999 (Asfaw et al., 1999). It was introduced to accommodate specimens recovered in 1997 from Aramis in the Middle Awash study area, Ethiopia. The hypodigm is presently restricted to fossils recovered from the Hata Member in the Middle Awash study area, Ethiopia. The type specimen, the *ca.* 2.5-Ma BOU-VP-12/130, combines a primitive cranium with large-crowned postcanine teeth. However, unlike *P. boisei* (see above), the incisors and canines are large and the enamel apparently lacks the extreme thickness seen in the latter taxon. A partial skeleton with a long femur and forearm was found nearby but is not associated with the type cranium, and it has not been formerly assigned to *Au. garhi.* If the type specimen of *P. aethiopicus* (Omo 18.18) belongs to the same hypodigm as the mandibles that seem to match the *Au. garhi* cranium, then *P. aethiopicus* would have priority as the name for the hypodigm presently attributed to *Au. garhi.*

**Possible Hominins**

This group includes taxa that may belong to the human clade. However, most of the taxonomic assignments reviewed below take little or no account of the possibility that cranial and dental features assumed to be diagnostic of the human clade (e.g., foramen magnum position and canine size and shape) may be homoplasies (see below). Thus, for the reasons set out in the next section, rather than assume these taxa *are* hominins, the prudent course is to consider them as *candidates* for being early members of the human clade.

The type specimen, ARA-VP-6/1, of the taxon now called *Ardipithecus ramidus* (White, Suwa, and Asfaw 1994) White, Suwa, and Asfaw 1995 (White et al., 1994, 1995) was recovered in 1993 from Aramis, in the Middle Awash study area, Ethiopia. All of the hypodigm come from the sites of Aramis, Kuseralee Dora, and Sagantole in the Central Awash Complex, Middle Awash study area, or from sites in the Gona study area, also in Ethiopia. The morphology of the Tabarin is such that it, too, could belong to the *Ar. ramidus* hypodigm. The temporal range of *Ar. ramidus* is *ca.* 4.5–4.3 Ma. The published evidence consists of two associated skeletons, one of which (ARA-VP-6/500) includes a partial skull and especially good preservation of the hands and feet, a piece of the base of the cranium, mandibles, associated dentitions, isolated teeth, two vertebrae, a first rib, fragments of long bones, and other isolated postcranial fossils. The

remains attributed to *Ar. ramidus* share some features in common with living species of *Pan,* others that are shared with the African apes in general, and several dental and cranial features that it is claimed are shared only with later hominins, such as *Au. afarensis.* Thus, the discoverers have suggested that the taxon belongs within the human clade (White et al., 2009). The body mass of the presumed female partial skeleton has been estimated to be *ca.* 50 kg, the canines are claimed to be less projecting than those of common chimpanzees, and the degree of functional honing is modest. The postcanine teeth are relatively small, and the thin enamel covering on the teeth suggests that the diet of *Ar. ramidus* may have been closer to that of chimps/bonobos than to later hominins. Despite having ape-like hands and feet, the position of the foramen magnum and the reconstruction of the poorly preserved pelvic bone have been interpreted as confirmation that *Ar. ramidus* was an upright biped.

The type specimen of the taxon *Orrorin tugenensis* Senut et al. 2001 is BAR 1000'00, a fragmentary mandible, recovered in 2000 from the locality called Kapsomin at Baringo in the Tugen Hills, Kenya. The 13 specimens in the hypodigm all come from four *ca.* 6-Ma localities in the Lukeino Formation. The morphology of three femoral fragments has been interpreted as suggesting that *O. tugenensis* is an obligate biped (Senut et al., 2001; Richmond and Jungers, 2008), but other researchers interpret the radiographs and CT scans of the femoral neck as indicating a mix of bipedal and nonbipedal locomotion (Ohman et al., 2005). Otherwise, the discoverers admit that much of the critical dental morphology is "apelike" (Senut et al., 2001).

*Sahelanthropus tchadensis* Brunet et al. 2002 is the taxon name given to fossils recovered in 2001 from the *ca.* 7-Ma Anthrocotheriid Unit at Toros-Menalla, Chad. The type specimen is TM266-01-060-1, a plastically deformed adult cranium, and the rest of the small hypodigm consists of mandibles and some teeth; there is no published postcranial evidence. *S. tchadensis* is a chimp/bonobo-sized animal displaying a novel combination of primitive and derived features. Much about the base and vault of the cranium is chimp/bonobo-like, but the relatively anterior placement of the foramen magnum is hominin-like. The supraorbital torus, lack of a muzzle, apically worn canines, low, rounded, molar cusps, relatively thick tooth enamel, and relatively thick mandibular corpus all suggest that *S. tchadensis* does not belong in the *Pan* clade (Brunet et al., 2002).

The most recently recognized taxon in the "possible hominin" grade category is *Ardipithecus kadabba* Haile-Selassie, Suwa, and White 2004 (Haile-Selassie, 2001; Haile-Selassie et al., 2004). The new species was established to accommodate cranial and postcranial remains announced in 2001 and six new dental specimens announced in 2004. All of the hypodigm were recovered from five *ca.* 5.8–5.2-Ma localities in the Middle

Awash study area, Ethiopia. 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 that of *Ar. ramidus.* Haile-Selassie et al. (2004) suggest that there is a morphocline in upper canine morphology, with *Ar. kadabba* exhibiting the most ape-like morphology and *Ar. ramidus* and *Au. afarensis* interpreted as becoming progressively more like the lower and more asymmetric crowns of later hominins. The proximal foot phalanx (AME-VP-1/71) combines an ape-like curvature with a proximal joint surface that is like that of *Au. afarensis* (Haile-Selassie, 2001). These four taxa could be primitive hominins, but they could also belong to separate clades of apes that share homoplasies with the human clade.

## CHALLENGES

### Differences Between an Early-Hominin Taxon and a Taxon in a Closely Related Clade

The differences between the skeletons of living modern humans and their closest living relatives, common chimpanzees and bonobos, are particularly marked in the brain case, dentition, face and base of the cranium, and in the hand, pelvis, knee, and the foot. But the differences between the *first,* or stem, hominins and the *first,* or stem, panins were likely to have been much more subtle. In what ways would the earliest hominins have differed from the last common ancestor (LCA) of chimps/bonobos and modern humans, and from the earliest panins? Compared with panins they would most likely have had smaller canine teeth, larger chewing teeth, and thicker lower jaws. There would also have been some changes in the skull, axial skeleton, and the limbs linked with more time spent upright and with a greater dependence on the hind limbs for bipedal locomotion. These changes would have included, among other things, a forward shift in the foramen magnum, adjustments to the pelvis, habitually more extended knees, and a more stable foot.

But all this assumes there is no homoplasy (see below) and that the only options for a 8–5-Ma African higher primate are being the LCA of modern humans and chimps/bonobos, a primitive hominin, or a primitive panin. It is, however, also possible that such a creature may belong to an extinct clade (e.g., a sister taxon of the LCA of modern humans and chimps/bonobos, or the sister taxon of the earliest hominins or panins).

**Species Recognition in the Hominin Clade**

It is difficult to apply process-related species definitions to the fossil record (Smith, 1994). Most paleoanthropologists use one version or other, of one of the species concepts in the pattern-related subcategory [i.e., the phenetic species concept (PeSC), the phylogenetic species concept (PySC), or the monophyletic species concept (MSC)]. These concepts all focus on an organism's hard-tissue phenotype (thus they are sometimes referred to as morphospecies concepts), but each of the concepts emphasizes a different aspect of the phenotype. The PeSC as interpreted by Sokal and Crovello (1970) gives equal weight to *all* aspects of the phenotype. It is based on a matrix that records the expression of each phenotypic character for each specimen, and then multivariate analysis is used to detect clusters of individual specimens that share the same, or similar, character expressions. In contrast, the version of the PySC introduced by Cracraft (1983) emphasizes the unique suite of derived and primitive characters that defines each species. According to Nixon and Wheeler (1990) in such a scheme a species is "the smallest aggregation of populations diagnosable by a unique combination of character states." The problem with the third species concept in the pattern-related subcategory, the MSC, is that it assumes researchers know which characters are uniquely derived. But to know this you must have performed a cladistic analysis (see below), and to do that you must have already decided on the taxa to include in the analysis.

In practice most paleoanthropologists use one or another version of the PySC. They search for the smallest cluster of individual organisms that is "diagnosable" on the basis of the preserved morphology, and then they seek to recognize taxa that embrace the levels of variation that are seen in living taxa. So why do competent researchers disagree about how many species should be recognized within the hominin fossil record? Researchers who favor a more anagenetic (or gradualistic) interpretation of the fossil record tend to stress the importance of continuities in the fossil record and opt for fewer species, whereas researchers who favor a more cladogenetic (or punctuated equilibrium) interpretation of the fossil record tend to stress the importance of discontinuities within the fossil record and opt for more speciose taxonomic hypotheses. These latter interpretations are referred to as *taxic* because they stress the importance of taxonomy for the interpretation of evolutionary history. But when all is said and done a taxonomy is just a hypothesis; it is not written on stone tablets.

## Recognizing and Coping with Homoplasy in and Around the Hominin Clade

Homoplasy—that is, shared characters not inherited from the most recent common ancestor of the taxa that express them—complicates attempts to reconstruct phylogenetic relationships because homoplasies give the impression that two taxa are more closely related than they really are. There are many aspects of morphology that might represent homoplasy in the hominin clade. The genus *Paranthropus* is based primarily on craniofacial morphology that suggests an adaptation to feeding on hard or abrasive foods. These features include postcanine megadontia, thick enamel, and changes to the zygomatic and other cranial bones that result in an improved mechanical advantage for chewing on the postcanine tooth crowns. If these adaptations of the megadont archaic hominins were inherited from a recent common ancestor, then a separate *Paranthropus* genus *is* justified; however, if they occurred independently in the *P. aethiopicus* and *P. boisei* lineage in East Africa and in the *P. robustus* lineage in southern Africa, and thus were examples of homoplasy, then a separate genus would *not* be justified. Locomotor and postural adaptations of the postcranial skeleton are another possible source of homoplasy. It is generally assumed that bipedal locomotion, and the morphological changes it entails, arose only once during the course of hominin evolution. But there is no logical reason to exclude the hypothesis that bipedality arose more than once in the hominin clade (Wood, 2000); indeed the evidence that there may have been more than one pattern of limb proportions among the taxa within the archaic hominin grade (Green et al., 2007) lends support to at least some aspects of the hypothesis that bipedalism may be homoplasic within the hominin clade. Moreover, there is no a priori reason to conclude that facultative bipedalism was confined to the hominin clade.

What should the null hypothesis be with respect to homoplasy in the great ape part of the tree of life? Should similar characters be considered *homologous* until proven otherwise? Or is the possibility of homoplasy sufficiently likely that a more prudent null hypothesis would be that all similarites are considered at least as likely to be *homoplasies* as homologies? The extent of homoplasy in other mammalian lineages as well as in other primate groups suggests that homoplasy should be given more consideration than it has when developing taxonomic hypotheses about new great ape taxa.

## OPPORTUNITIES

### Advances in Data Capture

Obviously new fossil discoveries provide additional evidence about human evolution, but additional evidence can also be extracted from the existing fossil record. Ionizing radiation has been harnessed to provide images of the internal structure of fossil hominins for more than 70 years, but recently clinical imaging techniques in the form of computed tomography (CT) have been used to access hitherto unavailable morphology (Spoor et al., 2000). Techniques such as microCT (Kono, 2004), confocal microscopy (Bromage et al., 2005), and synchroton radiation microtomography (SR-μCT) (Tafforeau and Smith, 2007) have been used to image the internal macro- and microstructure of higher primates and hominin fossils (Smith and Tafforeau, 2008). MicroCT provides better images of small structures such as teeth than regular CT, and it is now being used to capture the detailed morphology of the enamel-dentine junction (EDJ) (Skinner et al., 2008a; Braga et al., 2010). This has a twofold advantage. First, it provides morphological information in 3D about the EDJ, a structure that was hitherto inaccessible without destructively sectioning a tooth crown, and second, by focusing on the morphology of EDJ it means that worn teeth, which may preserve very little in the way of detailed outer enamel surface morphology, can be used to generate information about the range of intraspecific variation in hominin fossil taxa (Skinner et al., 2008b).

All three of these imaging techniques have, and will, prove to be especially useful for helping to sort homoplasies from homologies. For example, what may superficially look like a dental homology (e.g., the possession of an apparently similar shared nonmetrical trait in two taxa) at the outer enamel surface may turn out to be a homoplasy if by using microCT it can be shown that it has significantly different manifestations at the EDJ (Skinner et al., 2009). Information about the ontogeny of dental enamel (e.g., enamel secretion rates, extension rates, the lifespan of ameloblasts) at the cellular level has been obtained from naturally or deliberately sectioned fossil teeth (Dean, 2000), and now both confocal microscopy (Bromage et al., 2005) and SR-μCT (Tafforeau and Smith, 2007; Smith and Tafforeau, 2008) can be used to investigate the dental microstructure of fossil teeth nondestructively. This means, for example, that it is possible to investigate whether the thick enamel shared by two hominin taxa has the same developmental basis (Lacruz et al., 2008). If its ontogeny is the same, then it is not possible to refute the hypothesis that the shared enamel thickness is a homology, but if the pattern of cellular activity involved in the ontogeny of the thick enamel *is* different

in the two taxa, then the hypothesis that thick enamel is a homology *can* be refuted.

## CONCLUSIONS

In the third essay in his *Evidence as to Man's Place in Nature,* Huxley (1863) discusses just two hominin fossils, the child's cranium from Engis and the adult cranium from the Kleine Feldhofer Grotte. Huxley's analysis of the two fossil crania is perceptive and prescient. He suggests that even though the Neanderthal remains are "the most pithecoid of known human skulls," he goes on to write that "in no sense ... can the Neanderthal bones be regarded as the remains of a human being intermediate between Man and Apes," and he notes that if we want to seek "the fossilized bones of an Ape more anthropoid, or a Man more pithecoid" than the Neanderthal cranium, then researchers need to look "in still older strata" (p. 159).

Since 1863 much progress has been made in both the accumulation of fossil evidence germane to human evolution, in the techniques used to capture morphologic information from that fossil evidence, and in the methods used to analyze those data. To better understand our evolutionary history these three enterprises—the acquisition of new fossil evidence [e.g., Berger et al. (2010)], the extraction of data from that evidence, and its analysis—must all advance. Effective techniques for data acquisition and analysis in the absence of fossils and an abundance of fossil evidence in the absence of effective data acquisition and analytical techniques are of little value. We trust that when the time comes to celebrate the 150th anniversary of the publication of Darwin's *Descent of Man* in 2021, significant progress will have been made in all three of these endeavors.

## ACKNOWLEDGMENTS

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# 2

# Terrestrial Apes and Phylogenetic Trees

JUAN LUIS ARSUAGA

The image that best expresses Darwin's thinking is the tree of life. However, Darwin's human evolutionary tree lacked almost everything because only the Neanderthals were known at the time and they were considered one extreme expression of our own species. Darwin believed that the root of the human tree was very deep and in Africa. It was not until 1962 that the root was shown to be much more recent in time and definitively in Africa. On the other hand, some neo-Darwinians believed that our family tree was not a tree, because there were no branches, but, rather, a straight stem. The recent years have witnessed spectacular discoveries in Africa that take us close to the origin of the human tree and in Spain at Atapuerca that help us better understand the origin of the Neanderthals as well as our own species. The final form of the tree, and the number of branches, remains an object of passionate debate.

In *The Descent of Man*, Darwin (1871a) paid little attention to the only human fossils known at the time that were not modern humans, the Neanderthals. Only two references to them can be found in its pages,

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and one of them refers to the same fossil that gave its name to this form of humanity: "Nevertheless, it must be admitted that some skulls of very high antiquity, such as the famous one of Neanderthal, are well developed and capacious" (Darwin, 1871a, Vol. I, p. 146). The second reference to a Neanderthal fossil mentions the mandible from the Belgian site of La Naulette: "Considering how few ancient skulls have been examined in comparison with recent skulls it is an interesting fact that in at least three cases the canines project largely; and in the Naulette jaw they are spoken of as enormous" (Darwin, 1871a, p. 126). Darwin had actually held the Forbes' Quarry Neanderthal skull from Gibraltar in his hands. This specimen was found in 1848, before the discovery in 1856 of the skeleton at the Feldhofer grotto in the Neander Valley for which the species *Homo neanderthalensis* (or subspecies, *Homo sapiens neanderthalensis,* according to some researchers) was named. In a letter to J. D. Hooker dated September 1, 1864, Darwin wrote: "F. (Falconer) brought me the wonderful Gibraltar skull" (Menez, 2009). The reason behind Darwin's lack of interest in the Neanderthals may stem from the judgment made previously of these same specimens by Thomas Henry Huxley in his *Evidence as to Man's Place in Nature* in 1863: "the Neanderthal cranium is by no means so isolated as it appears to be at first, but forms, in reality, the extreme term of a series leading gradually from it to the highest and best developed of human crania."

Darwin was in search of a "missing link," a transitional form between modern humans and the chimpanzee or gorilla. At that time, a fossil fulfilling the role of linking two large zoological groupings had already been found. *Archaeopteryx* was incorporated into the third edition (1866) of *The Origin of Species:* "and still more recently, that strange bird, the Archeopteryx, with a long lizard-like tail, bearing a pair of feathers on each joint, and with its wings furnished with two free claws, has been discovered in the oolitic slates of Solenhofen. Hardly any recent discovery shows more forcibly than this how little we as yet know of the former inhabitants of the world." (Darwin, 1859, 1866)

The discovery of *Homo erectus* in 1891 in Java might have satisfied Darwin. Alternatively, he may have considered it too human and, with its reduced cranial capacity, only slightly more primitive than the Neanderthals. It is possible that the authentic missing link (or, more appropriately, "fossil link") for Darwin would have been the Taung child, discovered in 1924 and of such a primitive aspect that it took 20 years until it was finally accepted as our ancestor by the majority of the scientific community.

Darwin believed that the origins of humanity most likely lay in Africa, although the discovery of fossil apes in Europe made him question this. In *The Descent of Man* (Darwin, 1871a, p. 199) he reflects on the topic:

> It is therefore probable that Africa was formerly inhabited by extinct apes closely allied to the gorilla and chimpanzee; and as these two species are now man's nearest allies, it is somewhat more probable that our early progenitors lived on the African continent than elsewhere. But it is useless to speculate on this subject, for an ape nearly as large as a man, namely the Dryopithecus of Lartet, which was closely allied to the anthropomorphous Hylobates, existed in Europe during the Upper Miocene period; and since so remote a period the earth has certainly undergone many great revolutions, and there has been ample time for migration on the largest scale.

It is interesting to note that Darwin considered modern humans more closely related to chimpanzees and gorillas, African apes, than to orangutans and gibbons. This must have led him to include us with the African group and consequently to consider us at least as much an ape as the orangutans and gibbons, which had separated previously from a common root. We would therefore be a highly evolved form of African ape. The same resemblance between us and the African apes had been noted previously in 1863 by Huxley (1959): "It is quite certain that the Ape which most nearly approaches man, in the totality of its organization, is either the Chimpanzee or the Gorilla." Nevertheless, this did not lead Huxley to group us in the same taxonomic category with the African apes. Rather, it was they who were grouped with the other great ape, the orangutan, along with the lesser apes, the gibbons, in the same category: "The structural differences between Man and the Man-like apes certainly justify our regarding him as constituting a family apart from them."

The only way that modern humans are included within the group of apes, in which we are considered apes, is if we are more closely related phylogenetically to some of them (the African apes) than to others (the Asian apes). If this were not the case, the apes would form one clade (a natural group with an exclusive common ancestor) and we would form another, the human clade (sister group), connected with them at a lower node. This is what Darwin believed (1871a, p. 197):

> If the anthropomorphous apes be admitted to form a natural sub-group, then as man agrees with them, not only in all those characters which he possesses in common with the whole Catarhine group, but in other peculiar characters, such as the absence of a tail and of callosities and in general appearance, we may infer that some ancient member of the anthropomorphous sub-group gave birth to man. It is not probable that a member of one of the other lower sub-groups should, through the law of analogous variation, have given rise to a man-like creature, resembling the higher anthropomorphous apes in so many respects. No doubt man, in comparison with most of his allies, has undergone an extraordinary

> amount of modifications, chiefly in consequence of his greatly developed brain and erect position.

However, how could we be closer to chimpanzees and gorillas than to orangutans and gibbons and not share an exclusive common ancestor (which is not also common to the Asian apes) with them? There are two ways to explain this paradox. One of these is that Darwin and Huxley believed that the resemblances between apes and modern humans evolved in parallel. We just saw that Darwin did not believe much in the "law of analogous variation" when explaining our great similarity with apes, which he generally attributed to descent from a common ancestor. However, he did resort to parallel evolution to explain certain features:

> It must not be supposed that the resemblances between man and certain apes in the above and many other points—such as having a naked forehead, long tresses on the head, etc.—are all necessarily the result of unbroken inheritance from a common progenitor thus characterized, or of subsequent reversion. Many of these resemblances are more probably due to analogous variation, which follows, as I have elsewhere attempted to show, from co-descended organisms having a similar constitution and having being acted on by similar causes inducing variability.
>
> (Darwin, 1871a, p. 194)

It is not easy, then, to decide if Darwin attributed our great similarity with the great apes (which he recognized as being greater than with the lesser apes), and in particular with the chimpanzee and gorilla, to parallel evolution.

The other explanation is that both Darwin and Huxley maintained the separation between the apes (greater and lesser) on the one hand and humans on the other as a separate branch, on the basis of a notion of evolutionary grade, that is, resemblance between different species of ape, even while realizing that this was not a natural classification. Nevertheless, Darwin (at least according to certain researchers) was a proponent of classification based on genealogy (Eldredge and Cracraft, 1980). In *On the Origin of Species* (Darwin, 1859, 1866), he writes: "We can understand why a species of a group of species may depart, in several of its most important characteristics, from its allies, and yet be classed with them."

Nevertheless, Darwin does not seem to have recognized our common origin with the African apes because he drew, on April 21 in 1868, a schematic genealogical tree of the primates (Fig. 2.1) that was never published, but that corresponds with the classification he used in 1871 in *The Descent of Man.* Interestingly, the human lineage does not occupy the central axis of radiation of the primates, an eloquent confirmation of his vision of

evolution as nonteleological. At the same time he relates us closely with the apes, albeit as a separate group. Even the gibbons are slightly more closely related with the chimpanzees and gorillas than with humans.

Looking more closely at the drawing, we see numerous entries that are crossed out but they can still be discerned. Surprisingly, the gibbons were initially placed as the closest to humans, with the African apes further removed. These respective positions were subsequently changed so that the chimpanzee and gorilla are closer to humans, although they do not share a common ancestor with us. Did Darwin know that we *are* African apes (members of the same clade) but not dare to say it? It does not seem so, on the basis of the existence of the drawing, which he kept to himself. Might it be better to say he *did not dare to think it*? It is more likely that he simply gave greater importance to the enormous differences between modern humans—as a "consequence of his greatly developed brain and erect position" (Darwin, 1871a, p. 197)—and apes than to the similarities between modern humans and African apes. The truth is that without clearly separating primitive and derived features it is not possible to carry out a phylogenetic analysis, and neither Darwin nor T. H. Huxley went further in this regard than other evolutionary biologists of the time.

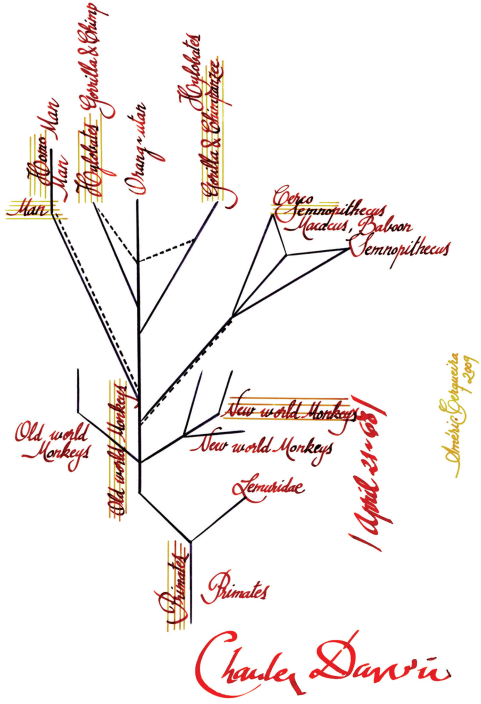


FIGURE 2.1 Transcription of the genealogical tree of primates in Darwin's sketch of 1868. Original is in The Complete Work of Charles Darwin Online: http://darwin-online.org.uk/. Identifier: CUL-DAR80, image 107.

Years before the fundamental work of W. Hennig (1966), *Phylogenetic Systematics*, was published in English, W. E. Le Gros Clark (1959), had already distinguished between "characters of common inheritance" (i.e., primitive characters or plesiomorphies, in cladistic jargon) and "characters of independent acquisition" (derived characters or apomorphies). According to Le Gros Clark, in spite of sharing many primitive features with the great apes, the australopithecines are classified within the hominids on the basis of sharing a few derived characters. Although their grade was largely ape-like, the australopithecines already belonged to the human clade. "Since the pongid sequence of evolution has been much more conservative than the progressive hominid sequence, its terminal products (the modern anthropoid apes) have preserved more of the original characters of the ancestral stock. As divergent evolution proceeds, characters of common inheritance will become progressively supplemented or replaced by characters of independent acquisition in each line" (Le Gros Clark, 1959). The australopithecines, then, were recognized as primitive ancestors of our own species, and both Raymond Dart (the discoverer of the Taung child) and Darwin were vindicated. Finally, a missing link connecting humans with the great apes had been provided, but with which ones: All of the apes in general, only with the great apes, or only with some of the great apes in particular?

That modern humans shared some derived features only with African apes (but not the orangutans) was not realized at the time by Le Gros Clark. But things would soon change. At a summer conference in 1962 organized by the Wenner-Gren Foundation, three biologists presented the results of studies that grouped modern humans with African apes in particular and excluded orangutans and gibbons. The evidence relied upon was both cytogenetic (Klinger et al., 1963) and molecular: serum proteins (Goodman, 1963a) and hemoglobin (Zuckerkandl, 1963). In fact, the study of chromosomes went even further because it showed a closer relationship between modern humans and chimpanzees than between chimpanzees and gorillas, but Morris Goodman had published his results one year earlier (Goodman, 1962b).

George Gaylord Simpson, Theodosius Dobzhansky, and Ernst Mayr, all present at the conference, accepted the inclusion of humans in the African ape clade. However, the great primatologist Adolph H. Schultz (1963) continued to consider the great apes as forming a clade that excluded humans, who had branched off previously (more or less at the same time as the hylobatids and certainly before the orangutans separated from the African apes): "Such evidence [`of extremely close similarities between man and chimpanzee and (or) gorilla'], although of greatest interest, is more than counterbalanced by the mass of profound differences found in all sorts of other characters of recognized reliability." On the other hand, Simpson

(1963) preferred to maintain the division between pongids (divided into hylobatines and pongines) and hominids (in spite of clearly realizing this was not a natural or phylogenetic classification) mainly on the basis of notions of evolutionary grade. The human line occupied a new adaptive zone that warranted its own family, even though the pongids were a paraphyletic group. According to Simpson, this will inevitably occur when a new family emerges from an old one: "Classification cannot be based on recency of common ancestry *alone*." Today some authors still use the term hominid—in the traditional way—to refer to all taxa of the human lineage after its separation from chimpanzees, whereas other authors prefer to call them hominins.

## HUMAN ORIGINS AND QUANTUM EVOLUTION

Once Darwinism (in the strict selectionist sense) was returned to a central place in evolutionary theory, the neo-Darwinians could turn their attention to other matters. The paleontologist G. G. Simpson distinguished in 1944 three patterns of evolution based on the fossil record: speciation, phyletic evolution, and quantum evolution. The first was responsible for the appearance of the lower taxonomic categories and explained the enormous proliferation of species that exist in the biosphere. The second produced the intermediate-level taxonomic categories and accounted for the evolutionary tendencies that paleontologists found everywhere when organizing fossils in progressive series that seemed to reflect gradual and directional changes. The third pattern was the cause of large-scale changes in the adaptive types (biological designs or body plans) that were produced in relatively short periods of geological time and that gave rise to large evolutionary novelties in the highest-level taxonomic categories.

Quantum evolution, as its name suggests, seemed opposed to the fundamental idea of evolutionary synthesis (i.e., that natural selection governed evolution), because passing from one adaptive plateau to another implied a loss of fitness, and natural selection never favors the less adapted. Because of this, Simpson (1953) presented this mode of evolution in a more orthodox form, as a case of phyletic evolution that proceeded at a more rapid rate than normal (due to an increase in the selection pressure).

But already by 1950, at the Cold Spring Harbor Symposia on Quantitative Biology, Simpson (1950) did not use the term "quantum evolution," but rather considered human evolution to represent a "change from one adaptive type to another." To explain how a change from one adaptive plateau to another was possible, Simpson no longer held that a maladaptive valley had to be traversed. The intermediate forms could now enjoy the advantages of both adaptive types, the old one that was being aban-

doned and the new one to which it was directed (which raises the question as to why natural selection would keep pushing the intermediate forms toward the new, more specialized adaptive type). This is what happened in Simpson's favorite evolutionary example, that of horses passing from browsers to grazers, as well as in the postural changes in our ancestors: "The new feature, for which the specialization was adaptive, was the ability to graze, to eat harshly abrasive food. Nevertheless the ability to eat less abrasive food, to browse, was not thereby lost. The development of upright posture in man and utilization of the hands for manipulation, only, and not locomotion, perhaps provide a better example of specialization that broadened rather than restricted the general adaptive type" (Simpson, 1950).

Nevertheless, other attendees of the symposium did use the expression quantum evolution, and in a manner very close to its original meaning, to explain the origin of human bipedal posture. W. W. Howells (1950) argued: "It is true that bipedal walking was the more radical line of change. As Washburn says, this was undoubtedly a case of quantum evolution, a conceptual contribution of Simpson (1944)." According to S. L. Washburn (1950) "The derivation of this type from an ape is best regarded as a case of rapid or quantum evolution (Simpson, 1944)." For Washburn, the key was in the iliac blade and the gluteus maximus muscle: "The argument runs as follows: among apes who were living at the edge of the forests and coming to the ground, were some who had shorter ilia. These ilia had to be more bent back for obstetrical reasons and in some this carried gluteus maximus far enough so that it became effective in finishing extension. This started a new selection which favored bigger gluteus muscles and ilia still further bent."

In the australopithecines, the pelvis had already undergone the necessary changes for obligate bipedalism, but other parts of the skeleton reflected this new posture. The unavoidable question is whether the passing from a nonbipedal adaptive type (that of the common ancestor of humans and chimpanzees) to an obligate bipedal one (like the australopithecines) occurred directly and only once or whether a transitional form had previously existed with a generally primitive skeleton but with some particular key feature (perhaps in the iliac blade as suggested by Washburn) that made an early form of facultative bipedal locomotion, still compatible with some degree of life in the trees, possible.

Currently, there are three known genera that predate *Australopithecus* and that, according to their respective discoverers, are our ancestors and were facultative bipeds: *Sahelanthropus* (Brunet et al., 2002; Zollikofer et al., 2005), *Orrorin* (Senut et al., 2001; Pickford et al., 2002), and *Ardipithecus* (Lovejoy et al., 2009; White et al., 2009). To date, only a single preaustralopithecine pelvis has been recovered, belonging to the *Ardipithecus ramidus*

skeleton found at Aramis (Middle Awash, Ethiopia) and dated to 4.4 mya. According to the researchers who described the specimen, some features characteristic of the modern human pelvis that are strongly related to bipedal posture—because they permit abduction during walking—can already be appreciated and are also found in the australopithecines and later hominids: a short iliac isthmus, a slightly broadened and sagittally oriented ilium with a weak greater sciatic notch, and a strong, anterior inferior iliac spine formed by a separate ossification center. In addition, the pubic symphysis would have been superoinferiorly short, differing from the tall symphysis in chimpanzees.

The authors of the study of the skeleton of *A. ramidus* maintain that the common ancestor of humans and chimpanzees was not a brachiator like living chimpanzees, but "was probably a palmigrade quadrupedal arboreal climber/clamberer that lacked specializations for suspension, vertical climbing or knucle-walking" (White et al., 2009). It was also claimed that *A. ramidus* occupied a different ecological niche than extant chimpanzees because the study of stable isotopes has shown that they consumed some $C_4$ plants (a type mostly represented in East Africa by grasses and sedges) as part of their diet (~10–25%), whereas extant chimpanzees are almost pure $C_3$ (forest green plants) feeders.

Although bipedal posture had been established, it would have undoubtedly been a more primitive form than that of *Australopithecus.* The postcranial skeleton of *A. ramidus* is, in general, very different from that of *Australopithecus afarensis.* If *Australopithecus anamensis* resembles *A. afarensis* postcranially, and *A. ramidus* is the direct ancestor, the passage from one adaptive plateau to another would have occurred in a relatively short period, ≤200 kya (from 4.4 to 4.2 mya). Thus, we could speak of a rapid evolution, at least in comparison with the subsequent stability in the body plan, which would not change during at least the subsequent 2 million years of evolution. But it is also possible that the skeleton of *A. ramidus* from Aramis corresponds to a later population than the population (of the same species) that gave rise to *Australopithecus.* In this case, the mother and daughter species would have coexisted, implying that this transition is not an example of the phyletic mode of evolution but rather of speciation or ramification (branching evolution) and further, of a special type ["like a parental *Hydra* buds off young individuals" in the words of Eldredge and Cracraft (1980)], because only a part of the ancestral species would have given rise to the descendant.

## HEADS AND BODIES

The neo-Darwinians, in general, gave more weight to the phyletic mode of evolution and maintained a very lineal notion of human evo-

lution (Tattersall, 2000). Theodosius Dobzhansky (1975) wrote in 1962: "Following Weidenreich, Dobzhansky (1944) and Mayr (1950) entertained the hypothesis that only one human or pre-human species existed in any one territory at any one time level in evolutionary history." But some years had passed and Dobzhansky now admitted a dead-end branch in the human genealogy, that of the paranthropines, or robust australopithecines: "In view of Robinson's (1954) fairly convincing demonstration that two species of australopithecines may have lived in South Africa within a relatively short period of time, if not simultaneously, this hypothesis remains now probable only for the representatives of the genus *Homo.*" For Dobzhansky, anagenesis predominated over cladogenesis in human evolution: "Both cladogenetic and anagenetic changes took place in man's ancestry but the latter predominated. Mankind was and is a single inclusive Mendelian population and is endowed with a single, corporate genotype, a single gene pool." Whether or not the evolution of the genus *Homo* represents a single lineage (i.e., a single panmictic unit) that changes through time, passing through different evolutionary grades is a question that has been debated ever since, and it is the topic I deal with in the rest of this article.

Historically, most of the species of the genus *Homo* that have been proposed have been based on craniodental anatomy. The postcranial skeleton has barely played any role in the respective diagnoses, mainly because it is more poorly preserved in the fossil record. But we now have a sufficiently large sample to attempt a synthesis of evolutionary changes in the hominid (or hominin, as other authors prefer) body (Carretero et al., 2004) (Fig. 2.2). The results of this analysis, based on body plan, suggest very few species in the genus *Homo.* Why, then, should the cranium be privileged when classifying the hominids?

The first known hominid postcranial morphotype would then be that of *A. ramidus,* which could be the same (or not) as the other preaustralopithecines: *Ardipithecus kadabba, Orrorin tugenensis,* and *Sahelanthropus tchadensis.*

The subsequent morphotype would be that of the australopithecines and paranthropines, as well as *Homo habilis.* To this, we also have to add the surprising *Homo floresiensis* from the late Late Pleistocene (Brown et al., 2004). This morphotype is characterized by small stature, markedly wide relative width of the pelvis, and short legs. In fact, the poverty of the fossil record for the postcranial skeleton is such that the attribution of the australopithecine morphotype to *H. habilis* is based on only a single, very incomplete skeleton (OH 62 from Olduvai Gorge, dated to ~1.8 mya) that, craniodentally, preserves mainly the palate.

At a later point during the Early Pleistocene (now considered to begin at 2.6 mya), a morphotype appears within the genus *Homo* that is char-

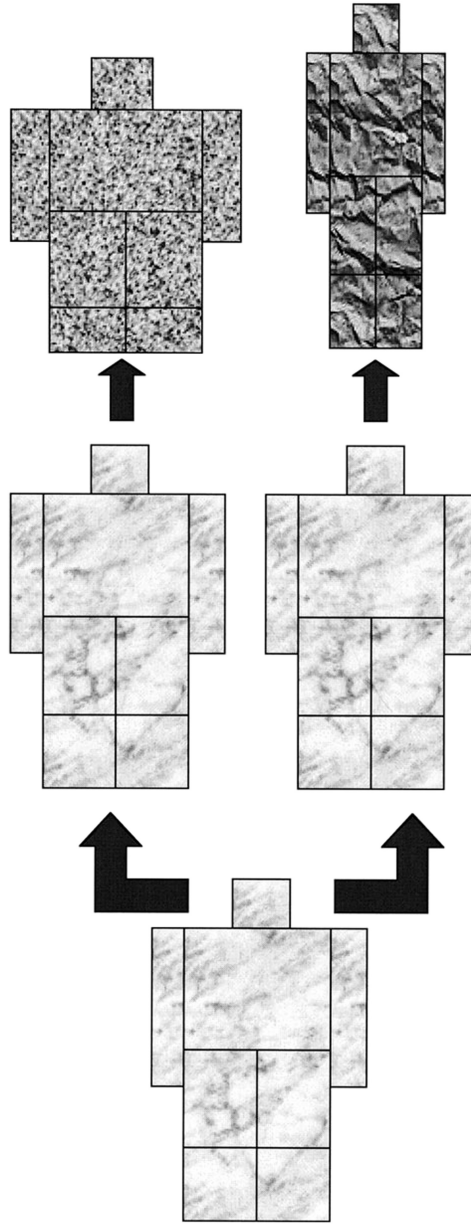

FIGURE 2.2 Changes in body shape in *Homo* (Carretero et al., 2004).

acterized by taller stature, long legs, and wide pelvis (although, relative to stature, not as wide as in the australopithecines). This change would have occurred in the species known either as *Homo ergaster,* a term that applies exclusively to African fossils, or *H. erectus,* a term that includes both the African specimens and Asian fossils from Java, where the species was defined, and Zhoukoudian (and some other sites) in China. The juvenile skeleton from Lake Turkana (KNM-WT 15000) dates to 1.5–1.6 mya and belongs to what we might call this "large hominid" to differentiate it from other earlier and contemporaneous specimens. There appears to have been a long period of coexistence of *H. habilis* and *H. ergaster* in East Africa, which would indicate not a lineal (anagenetic) evolutionary pattern, but a branching (cladogenetic) pattern of evolution. Some authors further recognize a third sympatric and synchronic species of *Homo*: *Homo rudolfensis.*

The tall and wide morphotype first seen in *H. ergaster/erectus* was maintained until the end of the Middle Pleistocene, when two new morphotypes appear. One, seen in modern humans, shows a narrower body cylinder and the other, seen in Neanderthals, shows a shortening of the distal segments of the extremities. The earliest (well-dated) modern human fossils are from Ethiopia and are represented by the skeleton of Omo I (~196 kya) (Pearson et al., 2008) and the crania from Herto (~150–160 kya) (White et al., 2003).

From the point of view of the postcranial skeleton, then, there would be only four morphotypes within the genus *Homo*, although the fossils from Dmanisi (Lordkipanidze et al., 2005, 2007; Rightmire et al., 2006) in Georgia (~1.75 mya) might represent an intermediate form between the primitive, australopithecine, morphotype of *H. habilis* and the tall and wide morphotype of *H. ergaster/erectus.* The skull of *Homo georgicus* is morphologically intermediate between *H. habilis* and *H. ergaster* or, alternatively, is a primitive form of the latter, which some authors, in turn, consider to be a primitive grade within *H. erectus.*

In reality, however, postcranial remains are abundant only at the Middle Pleistocene site of the Sima de los Huesos in the Sierra de Atapuerca, dated to at least 530 kya. Nevertheless, the isolated fossils from other sites such as the East African pelvises KNM-ER 3228 (perhaps older than the Turkana Boy) and OH 28 (<1.0 mya) as well as the Middle Pleistocene skeleton from Jinniushan in China (Rosenberg et al., 2006) do not differ from those at the Sima de los Huesos.

This overview has necessarily glossed over numerous details. Although living modern human populations are considered "tall hominids" compared with the early hominids, a wide variation in stature exists across the globe today. In Africa alone, there are modern human populations with average male stature <150 cm and others with averages ~180 cm.

This variation in height could have also characterized human species in the past. A recently published pelvis from the site of Gona in Ethiopia (Simpson et al., 2008) dates to 0.9–1.4 mya and shows a very wide maximum width between the iliac crests. At the same time, the size of the acetabulum indicates a very small body, like the australopithecines and paranthropines. Although this specimen has been attributed to *H. erectus,* its chronology, geographic location, and some aspects of its anatomy are also consistent with an assignment to *Paranthropus boisei* (Ruff, 2009a). If it represents *H. ergaster/erectus,* it would have to be a very small-bodied population, considerably smaller than living pygmies.

The size of the brain is not without importance in hominid taxonomy, and it has been extensively used. In principal component analyses of neurocranial variables, the first factor is always size (by far explaining the most variation) and this is strongly correlated with brain volume. Standardizing the raw values for size does not solve the problem because there is a tight relationship between size and shape. That is, most of the differences in the neurocranial architecture of fossils attributed to *Homo* are simply related to the size of the brain. Other features used in taxonomy are related to bone thickness, cranial superstructures (e.g., tori), or more or less subtle features of the temporal bone.

However, this is not always the case. Neanderthals and modern humans show similar cranial capacities but differ markedly in neurocranial morphology. The brain of *Homo sapiens* seems to follow a very different pattern from that of other species (Bruner et al., 2003). At the same time, some of the *H. erectus* fossils from Ngandong (Java) have cranial capacities similar to that of Cranium 5 from the Sima de los Huesos but the neurocranial anatomy is very different.

Consideration of the neurocranium, then, should complement the study of the postcranial morphotype. When brain size is related to body size using allometric equations (to eliminate the size factor), an encephalization curve is obtained that can be used for systematics (Arsuaga and Martínez, 2001). Compared with the australopithecines, *H. habilis* shows an increase in encephalization because the brain size increases whereas the body size does not. The shift to the subsequent cranial and postcranial combined morphotype (which starts with *H. ergaster/erectus)* involves an important increase in both brain size and body size, but the increase in encephalization is small. However, this may still indicate an advance in cognitive abilities. Comparison between chimpanzees and gorillas indicates that closely related species may show large differences in body size but little difference in brain mass and intelligence. In contrast, the cranial capacity in *H. ergaster/erectus* is much larger than that of the australopithecines.

Although the body cylinder does not differ among Middle Pleistocene fossils from Africa and Europe, an important brain expansion does occur by at least 500 kya, leading to a clear increase in encephalization. The range of cranial capacities from the Sima de los Huesos varies from 1,100 to 1,390 $cm^3$. Combining body size and shape and absolute and relative brain size, these Middle Pleistocene fossils represent a different morphotype from that of their Early Pleistocene ancestors as well as from that of Asian *H. erectus.* Those from Zhoukoudian in China have been dated to between 300 and 550 kya (Grün et al., 1997), but new dates using a different technique yielded much older results (~780 kya), at least for the lower levels (Shen et al., 2009). Thus, it is possible that by 500 kya, *H. erectus* survived only in Indonesia. The Neanderthals and modern humans show the highest encephalization because the increase in brain size is coupled with a decrease in body size, although by two different means. The Neanderthals underwent a shortening of the distal segments of the extremities, whereas *H. sapiens* shows a narrowing of the body cylinder.

In the middle of the Early Pleistocene at least two cranial and postcranial combined morphotypes coexisted, whereas during the late Middle and Late Pleistocene four morphotypes coexisted: that of Neanderthals, that of modern humans, the fossils from Ngandong (smaller brain size and assigned to a late population of *H. erectus*), and the australopithecine morphotype of *H. floresiensis.* If in the Late Pleistocene, when the fossil record is more complete, we find that four different human lineages coexisted, why not think that this has been the general trend?

It is important to point out here that, although this encephalization can be represented as a curve, it does not necessarily imply a steady, continuous rate of increase through time. In fact, body size, which is one of the variables involved in calculating the encephalization quotient, shows long periods of stability for each morphotype. Gould and Eldredge (1993) warn: "We have learned as a received truth of evolution, for example, that human brain size increased at an extraordinary (many say unprecedented) rate during later stages of our lineage. But this entrenched belief may be a chimera born of an error in averaging rates over both punctuations and subsequent periods of stasis." Hominid taxonomy within the genus *Homo* could be refined further if body size and shape and brain size were considered along with craniodental features.

## PALEONTOLOGICAL SPECIES

To approach a cranial analysis, I adopt a paleontological species definition based on an operational criterion: Two or more populations represent different paleontological species if the variation between them is clearly larger than the variation within each of them. Under these circumstances

it is relatively easy to recognize the affinities of an isolated specimen, something which would not be the case if the intrapopulation variation greatly exceeded the interpopulation variation.

The different geographic human populations alive today would clearly not be identified as different species using this criterion because it is very difficult to establish, visually, the geographic provenience of a modern human cranium (much less an isolated postcranial bone). However, in spite of the large overlap between the frequency distributions of local populations, certain differences do exist between the average values. Thus, it is possible to make a probable diagnosis of population affinity using a large number of cranial dimensions and relying on discriminant functions calculated on samples of known population affiliation. Nevertheless, in practice, the results of these analyses are often far from satisfactory.

One simple example comes from Ubelaker et al. (2002), who tried to classify the remains from a 16th–17th century ossuary near the city of Valladolid in the north of Spain. It is important to point out that this region of Spain was the least affected by the Arab incursions of the eighth century (which were primarily composed of Berbers from North Africa), so this population is unlikely to have been particularly heterogeneous. Twenty cranial measurements were taken on 95 individual skulls and compared, in turn, with the data in the Forensic Data Bank and with the collections studied previously by W. W. Howells (1989). In the first case, 29 individuals were classified as white, 40 as black, 17 as Hispanic, 2 as Chinese, 3 as Japanese, 2 as Amerindian, and 2 as Vietnamese. Using the Howells database, the 95 individuals were classified into 21 different groups.

Nevertheless, as Howells himself noted, a Neanderthal cranium is something else. It cannot be confused with a modern human, even at first glance. In this case, even the postcranial bones are often diagnostic. This criterion (variation between populations clearly larger than variation within each of them) can be applied to other hominoids, comparing, for example, the two chimpanzee species to one another or the different subspecies (or species, according to some researchers) of orangutans and gorillas, to determine the taxonomic level at which it is useful. At the same time, accumulating evidence from the Neanderthal genome has not documented any significant level of gene flow between them and us.

For authors who consider the Neanderthals to represent a subspecies of *H. sapiens* that appears at the end of the Middle Pleistocene in Europe, the last ancestral population (earlier in time, yet still undifferentiated) should also be called *H. sapiens* and it has been informally recognized as "archaic *H. sapiens*" (Stringer, 1992). If, on the other hand, the species *Homo neanderthalensis* is accepted, their last ancestor could still be *H. sapiens* (or the reverse) if the mode of speciation favored under the punctuated equilibrium model of evolution (i.e., with survival of the mother species)

is used. But the fossils from the early Pleistocene, as well as those of the early and middle Middle Pleistocene across the globe, are so different from Neanderthals and modern humans that a last common ancestor of a different species must be sought.

One available, although impractical, name is *Homo heidelbergensis*, with the Mauer mandible from Germany (~500 kya) as the holotype (Harvati, 2007). For some researchers, this is the last common ancestor, and it would have inhabited Europe, Africa, and perhaps even Asia (in more recent times than the *H. erectus* fossils from Zhoukoudian). The problem is that many researchers have recognized derived Neanderthal features, developed to a greater or a lesser degree, in the European middle Middle Pleistocene fossils, including the Mauer mandible, but not in the African specimens. These European specimens, then, could either be included within the species *H. neanderthalensis* (Hublin, 2009) or maintained as an earlier more primitive chronospecies, *H. heidelbergensis.*

One practical limitation in the previously mentioned criterion is that good samples of fossils are needed to compare the intra- and interpopulation variation. These kinds of samples are rare in paleoanthropology, unless fossils that span a considerable temporal and geographic range (and may therefore represent more than one species) are grouped together. However, this is not the case with the "classic" Neanderthals of the second half of the Late Pleistocene, which represent a relatively temporally and geographically restricted sample. Of course, the ideal situation would be to find contemporaneous fossils from the same geographic region and, if possible, even from the same site or geological strata.

The site of Dmanisi (Georgia) represents one of these rare circumstances. Another is in the Sierra de Atapuerca, where the site of the Gran Dolina, dated to ~900 kya (Berger et al., 2008), has yielded a sample of human fossils that to date represent a minimum of 11 individuals. Additional individuals may eventually be recovered given that the accumulation represents one or more episodes of cannibalism. These fossils have been designated a new species, *Homo antecessor* (Bermúdez de Castro et al., 1997), that predates *H. heidelbergensis* and is close to the last common ancestor of Neanderthals and modern humans. There are three mandibles and a parietal from the Algerian site of Ternifine (~700 kya) that have been designated *Homo mauritanicus* and could be the same species as those from the Gran Dolina (Hublin, 2001). However the Gran Dolina specimens are quite different (Bermúdez de Castro et al., 2007). The site of the Sima del Elefante, also in the Sierra de Atapuerca, has yielded a human mandible dated to 1.2–1.4 mya (Carbonell et al., 2008). In the near future, it will be possible to study the intraspecific variation within the sample from the Gran Dolina, but currently this type of study can only be carried out on a different sample from Atapuerca. At the Sima de los Huesos, a little less

than half of at least 28 individuals have been recovered, dating to >530 kya (Arsuaga et al., 1993, 1999; Bischoff et al., 2007). There are presently 17 crania and an equal number of mandibles in different states of reconstruction, ranging from complete specimens to more fragmentary remains (Figs. 2.3–2.6).

The fossils from the Sima de los Huesos are neither phenetically nor cladistically *H. sapiens.* When they are compared with Middle Pleistocene fossils from Zhoukoudian, from other parts of China, or in Java, they are also clearly not *H. erectus,* nor are they Neanderthals, but their sister group. Because the Mauer mandible is such an uninformative specimen, it is worth taking a closer look at the characteristics of this large collection of remains.

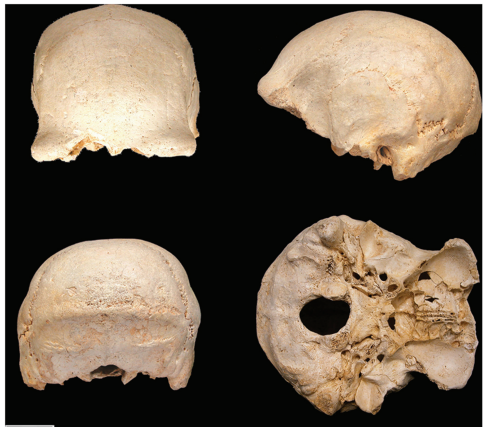

FIGURE 2.3 Sima de los Huesos (Atapuerca) cranium 4.

FIGURE 2.4 Sima de los Huesos (Atapuerca) cranium 5.

FIGURE 2.5 Sima de los Huesos (Atapuerca) cranium 6.

FIGURE 2.6 Sima de los Huesos (Atapuerca) cranium 14.

The population from the Sima de los Huesos can be identified by a combination of various types of features (Arsuaga et al., 1997; Martínez and Arsuaga, 1997):

(*i*) Features shared with Neanderthals and modern humans, but absent in *H. erectus.* Among these is a very convex superior border of the temporal squama.

(*ii*) Features that are neither plesiomorphies (they are not present in *H. erectus*) nor apomorphies of Neanderthals and modern humans, but intermediate character states that could give rise to one or the other.

For example, cranial wall sides slightly convergent upward or vertical (parallel) in rear view, which could transform into the high pentagonal shape displayed by *H. sapiens* as well as the rounded contour exhibited by *H. neanderthalensis.* In addition, the location of opisthocranion on the occipital plane of the occipital squama precedes the bulging occipital bones (although different in form) of Neanderthals and modern humans. These features are linked with a cranial capacity that is larger than that of *H. erectus* but smaller than in modern humans and Neanderthals.

(*iii*) Features exclusive to this and other European Middle Pleistocene populations. These features are not interpreted as a late stage in the transformation sequence of a derived character state but as intermediate character states in a postulated sequence of change (morphocline) that leads to the apomorphies of the Neanderthals. They are thus both primitive and derived. The anatomy of the occipital torus and that of the suprainiac area are a good example. The midface and the supraorbital torus are another.

(*iv*) Primitive features retained in *H. sapiens* but lost in the Neanderthals, such as the size and shape of the mastoid process.

(*v*) Primitive features lost in *H. sapiens* but retained in the Neanderthals, such as the absence of a chin.

(*vi*) Derived features unique to the Neanderthals (autapomorphies), such as the retromolar space of the mandible.

The postcranial skeleton, in particular the pelvis, is primitive and does not show the modifications from the archaic design seen in Neanderthals, such as the thin superior pubic ramus. In principle, autapomorphies have not been found in the Sima de los Huesos, which would exclude them from forming part of a chronospecies in the evolution of the Neanderthals, but this is because the unique features that are found (in this and other European middle Middle Pleistocene fossils) are interpreted as character states that are intermediate in their polarity. The amount of time between the fossils from the Gran Dolina (terminal Early Pleistocene) and the appearance of Neanderthals and modern humans (toward the end of the Middle Pleistocene) is sufficiently long (≥500 kyr) to be able to recognize other similar entities, like that at the Sima de los Huesos, in Europe or Africa.

Although we cannot compare the Sima de los Huesos with any other collection (because they do not exist), we can ask whether it is possible to find a fossil within the Sima de los Huesos sample with characteristics like those seen in the mandible of *H. antecessor* from the Gran Dolina or the Mauer mandible (Germany) or in the crania from Ceprano (Italy), Petralona (Greece), Swanscombe (England), or Broken Hill (Zambia). The fossil from Ceprano was even designated as a new species (*Homo cepra-*

*nensis*) when it was thought to be contemporaneous with the fossils from the Gran Dolina (Mallegni et al., 2003). It is now considered to be a possible contemporary of the Sima de los Huesos population (Muttoni et al., 2009).

Let me be clear. There is no fossil in the Sima de los Huesos that could be confused with Ceprano. The same could be said for Broken Hill, Arago, or Mauer. Others, including Swanscombe, Reilingen, Steinheim, and Petralona are more similar, but not the same. Reilingen, for example, already shows an "en bombe" profile (Schwartz and Tattersall, 2002) and the Petralona extraordinary sinuses in the face and the supraorbital torus are out of the Sima de los Huesos range of variation. It is my impression that if these other sites had yielded more fossils, they would be essentially the same as those already known (i.e., there would be more remains of "cepranensis," "petralonensis," and "swanscombensis," etc.) as occurred in the Sima de los Huesos and happens in any living human population, even across the entire species. If this is correct, and we may know when there are additional samples discovered, we would have other "entities" like the Sima de los Huesos. What taxonomic category should these hypothetical entities be given? Relying on the criterion of inter- vs. intrapopulation variation, they should be given that of species. If that of demes (subspecies) is preferred, it should be borne in mind that they would be demes of a strongly polytypic species, much more so than modern humans and perhaps more so than any of the extant hominoid species.

If we also have a fine chronological control for these entities, it would be possible to establish whether the evolutionary pattern that led to Neanderthals and modern humans was characterized by anagenesis or by successive speciation events. On the basis of the current state of our knowledge, reducing the human variability in Europe and Africa from the late Early Pleistocene to the middle Middle Pleistocene to a single species seems to be an exaggerated simplification.

## ACKNOWLEDGMENTS

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# 3

# Phylogenomic Evidence of Adaptive Evolution in the Ancestry of Humans

MORRIS GOODMAN*†‡ AND KIRSTIN N. STERNER*

In Charles Darwin's tree model for life's evolution, natural selection adaptively modifies newly arisen species as they branch apart from their common ancestor. In accord with this Darwinian concept, the phylogenomic approach to elucidating adaptive evolution in genes and genomes in the ancestry of modern humans requires a well-supported and well-sampled phylogeny that accurately places humans and other primates and mammals with respect to one another. For more than a century, first from the comparative immunological work of Nuttall on blood sera and now from comparative genomic studies, molecular findings have demonstrated the close kinship of humans to chimpanzees. The close genetic correspondence of chimpanzees to humans and the relative shortness of our evolutionary separation suggest that most distinctive features of the modern human phenotype had already evolved during our ancestry with chimpanzees. Thus, a phylogenomic assessment of being human should examine earlier stages of human ancestry as well as later stages. In addition, with the availability of a number of mammalian genomes, similarities in phenotype between distantly related taxa should be explored for evidence of convergent or parallel adaptive evolution. As an example, recent phylogenomic evidence has shown that adaptive evolution of aerobic energy metabolism genes may have helped shape such distinc-

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tive modern human features as long life spans and enlarged brains in the ancestries of both humans and elephants.

Charles Darwin (1859) proposed that natural selection favors inherited modifications that better adapt the organisms of a species to the environment of that species. Darwin also proposed the tree model for life's evolution. In this model, natural selection adaptively modifies newly arisen species as they branch apart from their common ancestor (Darwin, 1859). Although there is now evidence that symbiotic merges produced the first eukaryotes and that prokaryotic species engage in reticulate evolution (Doolittle, 1999; Margulis and Sagan, 2002; Avise, 2008), Darwin's model of tree-like branching appears to hold for the evolution of primates and other vertebrates. Having deduced that species share common ancestors, Darwin also reasoned that a truly natural system for classifying species would be genealogical, that is, species should be classified according to how recently they last shared a common ancestor. The hierarchical ranking in such a genealogical system could then be used to indicate how relatively close or distant in geological time extant species are from their last common ancestor (LCA).

In accord with this Darwinian framework, the phylogenomic approach to elucidating adaptive evolution in the ancestry of modern humans involves identifying the changes in genes and genomes on a phylogenetic tree that accurately places humans within the order Primates and, more widely, within the class Mammalia. Viewing the ancestries of many mammals, not just the ancestry of modern humans, could provide examples of convergent adaptive evolution, which may point to specific categories of genetic changes that are associated with important phenotypic changes. This phylogenomic approach could help identify the positively selected genetic changes that shaped such distinctive modern human features as prolonged prenatal and postnatal development, lengthened life spans, strong social bonds, enlarged brains, and high cognitive abilities. In this article, we first briefly sketch out the historical background of ideas and findings that have led to phylogenomic studies of human evolution. We then highlight the concepts that motivate our own efforts and discuss how phylogenomic evidence has enhanced our understanding of adaptive evolution in the ancestry of modern humans.

## DARWIN'S VIEWS

In *The Descent of Man, and Selection in Relation to Sex*, Charles Darwin (1874) suggested that Africa was the birthplace for humankind. The fol-

lowing five passages encapsulate for us Darwin's thinking about the place of humans in primate phylogeny and about the uniqueness of modern humans.

> If the anthropomorphous apes be admitted to form a natural subgroup, then as man agrees with them, not only in all those characters which he possesses in common with the whole Catarhine group, but in other peculiar characters, such as the absence of a tail and of callosities, and in general appearance, we may infer that some ancient member of the anthropomorphous subgroup gave birth to man.
>
> (Darwin, 1874, p. 160)

> It is therefore probable that Africa was formerly inhabited by extinct apes closely allied to the gorilla and chimpanzee; and as these two species are now man's nearest allies, it is somewhat more probable that our early progenitors lived on the African continent than elsewhere.
>
> (1874, p. 161)

> In regard to bodily size or strength, we do not know whether man is descended from some small species, like the chimpanzee, or from one as powerful as the gorilla; and, therefore, we cannot say whether man has become larger and stronger, or smaller and weaker, than his ancestors. We should, however, bear in mind that an animal possessing great size, strength, and ferocity, and which, like the gorilla, could defend itself from all enemies, would not perhaps have become social: and this would most effectually have checked the acquirement of the higher mental qualities, such as sympathy and the love of his fellows. Hence it might have been an immense advantage to man to have sprung from some comparatively weak creature.
>
> (1874, p. 65)

> As far as differences in certain important points of structure are concerned, man may no doubt rightly claim the rank of a Suborder; and this rank is too low, if we look chiefly to his mental faculties. Nevertheless, from a genealogical point of view it appears that this rank is too high, and that man ought to form merely a Family, or possibly even only a Subfamily.
>
> (1874, p. 158)

> Nevertheless the difference in mind between man and the higher animals, great as it is, certainly is one of degree and not of kind.
>
> (1874, p. 130)

Darwin's application of the theory of evolution by natural selection to discussions of our own origins and place within nature laid the foundation for modern phylogenetic and phylogenomic studies of human evolution. He proposed that humankind originated from man-like apes (first quote) in Africa and that humans are most allied to chimpanzees and gorillas (second quote). Further, Darwin seems to have thought that our progenitors were more like chimpanzees than gorillas (third quote). Darwin challenged the then orthodox view that a whole taxonomic order, the Bimana, should consist of only one species, our own *Homo sapiens*. Instead, Darwin noted that genealogically, we humans should have no more than a family or even just a subfamily to ourselves (fourth quote), suggesting that Darwin might have been willing to have a family Hominidae that grouped modern humans with man-like apes. Moreover, Darwin also commented on the most widely cited example of human uniqueness, the modern human mind. He postulated that the difference between the modern human mind and the mind of other higher animals was one of degree, not of kind (fifth quote). Nearly a century after Darwin first proposed the theory of evolution by natural selection, molecular evolution emerged as a scientific field and molecular methods began to be used toward the study of human evolution. Molecular evidence inferred from proteins and DNA data generated during the past 50 years have vindicated Darwin's foresightedness and have decisively established that among living species, modern humans have their closest kinship to common and bonobo chimpanzees.

## USE OF MOLECULAR METHODS TO INFER OUR PLACE IN NATURE

More than 100 years ago, Nuttall (1904) observed that rabbit antiserum produced against human whole-blood serum yielded larger precipitates when mixed with serum from human, chimpanzee, or gorilla blood than from orangutan, gibbon, or other mammalian blood. Although Nuttall did not comment on the possible phylogenetic and taxonomic significance of his antihuman serum cross-reacting more strongly with chimpanzee and gorilla sera than with Asian ape sera, he did foresee a promising future for molecular studies of evolution (Nuttall, 1904).

By the middle of the 20th century, molecular biologists had established that DNA contained the genetic information for an organism and that nucleotide sequences in genes encoded the amino acid sequences of proteins. Immunologists could then deduce that a protein's antigenic divergencies among species reflected amino acid sequence divergencies, the sources of which were nucleotide sequence substitutions. An immunological method that was much improved over Nuttall's was used to

examine protein divergencies among primate and other mammalian species (Goodman, 1961, 1962a,b, 1963a,b). The observed protein divergencies, interpreted as genetic divergencies, challenged the reigning view (Simpson, 1963) that the human lineage diverged markedly from the ancestral ape state to occupy an entirely new structural-functional adaptive zone. Whereas the then-prevailing view placed chimpanzees and gorillas with orangutans in the family Pongidae, with humans alone among living species in the family Hominidae (Simpson, 1963), the immunologically detected genetic affinities showed humans, chimpanzees, and gorillas to be highly similar and more closely related to one another than to orangutans or other primates, thus supporting chimpanzees and gorillas being grouped with humans in the family Hominidae (Goodman, 1962b, 1963a,b). The indicated genetic kinship between chimpanzees and gorillas was not any closer than the close kinship of either to humans. Indeed some immunological results placed chimpanzees closer to humans than to gorillas [e.g., Fig. 4 in Goodman (1963a)], and they also suggested that rates of molecular evolution had slowed in hominoid lineages (Goodman, 1961, 1962a,b, 1963a). Thus, these first substantial molecular data did not support the claim that the human lineage had diverged radically from an ancestral ape state. Instead, in their proteins, humans, chimpanzees, and gorillas diverged only slightly from one another. The degrees of interspecies antigenic divergence of serum albumin challenged the conventional view that many millions of years of evolution separated modern humans from our nearest nonhuman relatives (Sarich and Wilson, 1967a,b). Instead, when these immunologic divergence data were analyzed by a molecular clock model, the LCA of humans, chimpanzees, and gorillas was placed at only 5 Mya (Sarich and Wilson, 1967a,b).

The determination of the actual amino acid sequences of proteins began in the 1950s (Sanger and Thompson, 1952) and, in the ensuing decades, provided important information about human evolution. Phylogenetic analysis of hemoglobin amino acid sequences pointed to the possibility that chimpanzees and humans were more closely related to each other than either was to gorillas (Goodman et al., 1971, 1982, 1983). This analysis grouped chimpanzee and gorilla with human rather than with orangutan hemoglobin (Goodman et al., 1982, 1983) and showed human and chimpanzee hemoglobin to be identical and slightly divergent from gorilla hemoglobin (Goodman et al., 1971, 1982, 1983).

Estimates of interspecies genetic similarities were also obtained by DNA-DNA hybridization data. An initial set of such data reported in 1972 (Hoyer et al., 1972), similar to the hemoglobin amino acid sequence data, suggested that instead of a human-chimpanzee-gorilla trichotomy, humans and chimpanzees shared the more recent common ancestor. During the 1980s, extensive DNA-DNA hybridization data clearly placed chimpan-

zees closer to humans than to gorillas (Sibley and Ahlquist, 1984; Caccone and Powell, 1989). Direct measurements of interspecies genetic similarities were provided by the actual nucleotide sequences of orthologous DNAs, each set of these DNA orthologues apparently having descended from the same genomic locus in the LCA of the examined contemporary species. By the late 1980s and early 1990s, phylogenetic analysis of such data greatly strengthened the evidence that chimpanzees (common and bonobo) have humans, not gorillas, as their closest relatives (Miyamoto et al., 1987; Bailey et al., 1992; Horai et al., 1992).

With the advent of next-generation sequencing technologies, genomic-level sequence data have provided strong evidence that chimpanzees are our closest living relatives and only slightly diverge from us (Wildman et al., 2003; Chimpanzee Sequencing and Analysis Consortium, 2005; Goodman et al., 2005; Elango et al., 2006; Patterson et al., 2006b; Ebersberger et al., 2007). Large amounts of nucleotide sequence data have also been used to infer the evolutionary relationships among almost all extant primate genera (Goodman et al., 2005; Fabre et al., 2009) and among the major clades of placental mammals (Hallström et al., 2007; Wildman et al., 2007; Prasad et al., 2008). These data reveal that rates of molecular evolution were slower in apes than in Old World monkeys and, within the ape clade, slower in chimpanzees than in gorillas and orangutans and slowest in the human lineage (Elango et al., 2006; Kim et al., 2006). This slowdown can be attributed to the decreased annual mutation rates that must have resulted from lengthened generation times. There may also have been selection for more efficient mechanisms of DNA repair and maintenance of genome integrity (Barja and Herrero, 2000).

A number of recent studies have used fossil calibration points and a variable-rate molecular clock to infer divergence dates across primate phylogeny [e.g., Yoder and Yang (2004), Raaum et al. (2005), Steiper and Young (2006), Fabre et al. (2009)]. Dates inferred from the fossil record and molecular data suggest the human–chimpanzee LCA is more recent than the LCA age for the species of a strepsirrhine genus (either lemuriform or lorisiform) and is close to the LCA age for the species of an Old World monkey genus such as *Macaca* or *Cercopithecus* or a New World monkey genus such as *Ateles* or *Callicebus*. This objective view of our species recalls Darwin's vision of our place in a genealogical classification of primates. However, these data suggest that, rather than having a mere subfamily to ourselves, we modern humans should perhaps have no more than a genus or just a subgenus to ourselves; that is, common and bonobo chimpanzees and modern humans would be the only extant members of either subtribe Hominina or genus *Homo* (Goodman, 1996; Goodman et al., 1998; Wildman et al., 2003). The rules (Hennig, 1966) for such an age-based genealogical classification are that each taxon should represent a clade, and clades at an

equivalent evolutionary age should be assigned the same taxonomic rank. An intragenus sister-grouping of humans and chimpanzees is concordant with the ages of origin of many other mammalian genera (Wildman and Goodman, 2004) and captures the close genetic correspondence of humans to chimpanzees. In accord with this close correspondence, chimpanzees are highly social, have simple material cultures, inhabit a wide range of habitats that range from forests to savannas, and have the ability to use rudimentary forms of language (Fouts and Mills, 1997; Savage-Rumbaugh and Fields, 2000; Whiten et al., 2001; McGrew, 2004; Pruetz and Bertolani, 2007; Sanz and Morgan, 2007).

## PHYLOGENOMIC ASSESSMENT OF BEING HUMAN

The extensive sequencing of genomes from primates (Fig. 3.1) and other vertebrates makes possible a phylogenomic search for the genetic basis of modern human traits. The close genetic correspondence of chimpanzees to humans and the relative shortness of our evolutionary separation from chimpanzees suggest that most of the adaptive evolution that produced the distinctive modern human phenotype had already

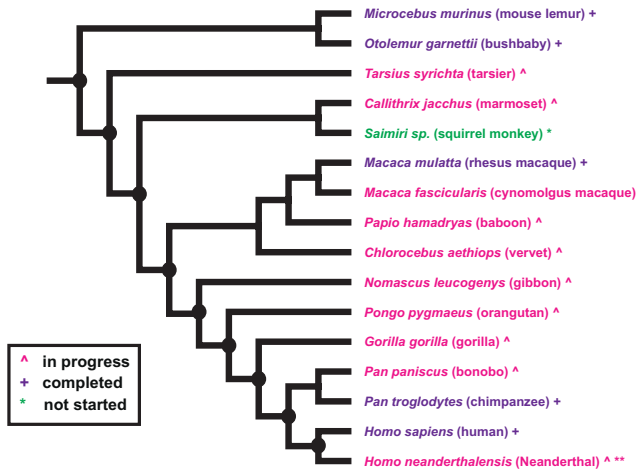



FIGURE 3.1 Summary of primate genome sequencing projects based on the National Human Genome Research Institute list of the status of approved sequencing targets (current as of December 15, 2009). Species with (+) are completed, (^) are in progress, and (*) has not yet been started. **Sequencing of the Neanderthal genome is currently in progress, although not listed by the National Human Genome Research Institute. Nodes of particular interest for examining the evolutionary origins of distinctive human traits are noted by a black oval.

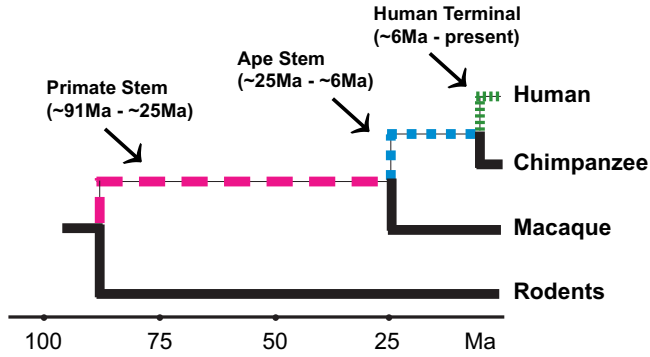



FIGURE 3.2 Lineages of interest when examining the evolutionary origins of distinctly human traits using currently available high-quality genomic data.

occurred by the time of the LCA of chimpanzees and humans. Thus, an assessment of the genetic underpinnings of being human should not just focus on the terminal human lineage but should also encompass earlier periods of human ancestry (Fig. 3.2). Moreover, there are other mammals with aspects of their phenotypes (e.g., enlarged brains) that are similar to aspects of the distinctive modern human phenotype. Examining the ancestries of these mammals is a further way to assess the genetic underpinnings of distinctive modern human phenotypic features and suggests that all such features are not necessarily unique to modern humans.

## PHYLOGENOMIC ASSESSMENT OF HUMAN BRAIN EVOLUTION REVEALS ADAPTIVE EVOLUTION IN MULTIPLE STAGES OF HUMAN ANCESTRY

Expanded cognitive abilities are hallmarks of modern humans. Why such abilities were selected for in modern humans and in the human lineage, and how they are maintained, is of great interest. As noted by Darwin more than 135 years ago, differences observed between the modern human mind and the mind of our closest living relatives can be more appropriately characterized as differences in degree, not differences in absolute kind. As such, we expect that the roots of the adaptive evolution that led to the modern human mind trace back to ancient stem lineages in primate and mammalian phylogeny. For example, humans have a phenomenal ability to design and use complex tools, but this ability depends on the opposable thumb, which had evolved in the early primates, as attested to by its presence in slow loris and other primate species.

A striking morphological feature that separates modern humans from other primates is our enlarged cerebral cortex. An initial enlargement of the cerebral cortex in the stem lineage of the anthropoid infra-order Catarrhini was followed by further marked enlargements in the hominid lineage to the chimpanzee/human LCA. After a period of stasis, a further marked expansion occurred during the past 3 million years in the terminal descent to modern humans. This last neocortical expansion resulted from more rapid and prolonged growth of brain mass. Whereas the chimpanzee brain reaches 40% of its adult size by the end of fetal life, the modern human brain at birth has reached only 30% of its adult size (DeSilva and Lesnik, 2008). Nevertheless, although far from its adult size, the newborn human brain is still larger than the newborn chimpanzee brain (DeSilva and Lesnik, 2008).

Anthropoid primates have large brains relative to body size, invasive hemochorial placentation, and long gestations. During this long gestation, the fetal brain consumes approximately 65% of the fetal body's total metabolic energy (Holliday, 1971). The invasive hemochorial placenta facilitates the transfer of nutrients from mother to fetus. Among anthropoids, modern humans have the largest brain, the most invasive placentation, and the longest gestation. In the earlier ancestry of humans, the threat of destructive maternal immune attacks on the fetus would have necessitated the evolution of mechanisms for immune tolerance at the maternal-fetal interface. Genes that code for galectins, proteins that promote immune cell death, may have provided the anthropoid fetus with an additional immune tolerance mechanism for averting maternal immune attacks (Than et al., 2009). Anthropoid primates have placental-specific galectins that induce apoptosis of T lymphocytes (Than et al., 2009). These genes originated from gene duplications that occurred in the anthropoid stem lineage, and then in that lineage, regulatory evolution of these genes produced placental-specific expression. Moreover, there was also positive selection for amino acid replacements in the placental galectins of the common ancestor of anthropoids, of catarrhines, and of humans. This adaptive evolution contributed to distinctive but not unique modern human features such as lengthened gestation and increased brain-to-body size ratio. Paradoxically, because of the selection that brought about distinctive modern human features, which also include prolonged postnatal development and longer generation times, we are genetically closer to the human/chimpanzee LCA than are chimpanzees (Elango et al., 2006; Kim et al., 2006; Wildman et al., 2007).

Potential genetic correlates to increased brain size in the primate lineage that descended to humans is provided by the evolutionary history of Abnormal Spindle-Like Microcephaly-Associated (*ASPM*) and microcephalin (*MCPH1*), two genes that have mutant forms associated with the

severe reduction of brain size that characterizes microcephaly in humans (Bond et al., 2002; Jackson et al., 2002). During descent of the ape stem portion of the primate lineage to humans (approximately 25 to 6 Mya), positive selection acted on microcephalin's protein-coding sequence, and during the past 6 million years in descent from the chimpanzee/human LCA to modern humans, positive selection acted on *ASPM*'s protein-coding sequence (Zhang, 2003b; Evans et al., 2004a,b; Kouprina et al., 2004; Wang and Su, 2004).

Language is also considered to be a distinctive human trait. There is evidence of accelerated evolution in the human terminal of the protein-coding sequence of Forkhead Box P2 (*FOXP2*) (Enard et al., 2002b; Zhang et al., 2002; Spiteri et al., 2007). This gene encodes a transcription factor that influences the expression levels of many brain-expressed genes. *FOXP2* mutants have been found in humans with language dysfunction (Lai et al., 2001; MacDermot et al., 2005; Feuk et al., 2006), suggesting that adaptive evolution of *FOXP2* may have contributed to the origin of modern human spoken language abilities (Enard et al., 2002b; Zhang et al., 2002). This adaptive evolution may have occurred in archaic humans ancestral to both Neanderthals and modern humans, an inference drawn from the finding that Neanderthal FOXP2 has the same two amino acid replacements that distinguish modern human FOXP2 from the orthologous chimpanzee protein (Krause et al., 2007). The chimpanzee FOXP2 patterns of brain transcriptional regulation differ somewhat from the modern human FOXP2 patterns (Konopka et al., 2009), although there is no direct evidence that the two-amino acid difference of chimpanzee FOXP2 from modern human FOXP2 causes language dysfunction. In addition to evidence suggesting *FOXP2* has evolved adaptively in humans, five of the genes that FOXP2 regulates had themselves been under positive selection (Konopka et al., 2009). Several genes involved in the development of the auditory system also show evidence of adaptive evolution in modern humans (A.G. Clark et al., 2003).

A number of recent studies have examined gene expression in the brain transcriptomes of different primate species. More expression changes were observed in the human brain than in other primate brains (Enard et al., 2002a). In general, the majority of these changes involved increased expression (Cáceres et al., 2003). Among the genes found to be up-regulated in modern humans are genes involved in neuronal activity and metabolic processes (Cáceres et al., 2003; Uddin et al., 2004). Genes involved in oxidative phosphorylation (electron transport) are especially up-regulated in humans (Uddin et al., 2004). Most recently, Nowick and colleagues (2009) suggested that major differences in expression of brain-expressed genes observed between human and chimpanzee may be coordinated by a small number of transcription factors that show differential expression

between humans and chimpanzees. Interestingly, many of these transcription factors are associated with pathways involved in energy metabolism (Nowick et al., 2009).

In addition to changes in gene expression level, gene duplication events during human ancestry may have also contributed significantly to our brain evolution. All mammals possess a gene that encodes glutamate dehydrogenase 1 (*GLUD1*). Whereas *GLUD1* is localized to both the mitochondria and cytoplasm where it functions in the metabolism of glutamate, a retrotransposon-mediated duplication event in the hominoid ancestor approximately 18 to 25 Mya (Burki and Kaessmann, 2004) resulted in a second GLUD-encoding gene (*GLUD2*) that is targeted specifically to the mitochondria (Rosso et al., 2008). Glutamate is the most common neurotransmitter in the brain. It is believed that positively selected amino acid substitutions in *GLUD2* allow for more efficient energy metabolism of glutamate in the brain (Plaitakis et al., 2000, 2003; Rosso et al., 2008).

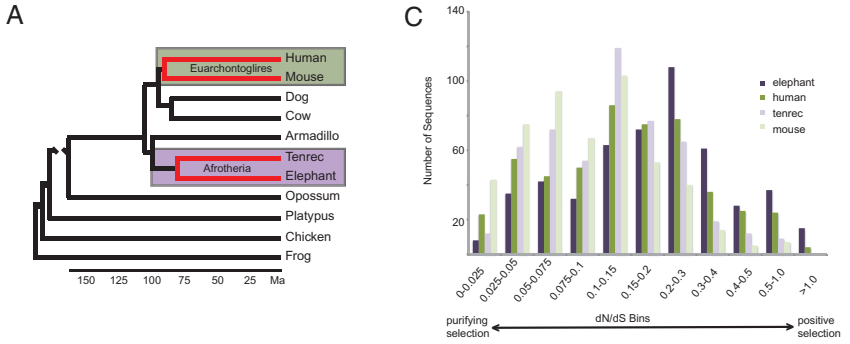
## AEROBIC ENERGY METABOLISM GENES AND BRAIN EVOLUTION

Neurons are the most energy-demanding cells of the modern human body (Attwell and Laughlin, 2001). The proliferation and pruning of neurons and their dendrites and the formation of the synaptic connections involved in learning are all energy-intensive processes. Thus it was not unexpected that aerobic energy metabolism (AEM) genes were found to be major targets of positive selection in the adaptive evolution of enlarged brains. This finding was made in a phylogenomic study that examined protein-coding sequence evolution during human ancestry (Uddin et al., 2008). In the time between the Old World monkey–ape LCA and the chimpanzee–human LCA, the most favored targets of positive selection were brain-expressed genes that code for mitochondrial functioning proteins, for example, proteins of the oxidative phosphorylation pathway (Uddin et al., 2008; Goodman et al., 2009). Although not brain-specific, many of these AEM genes are highly expressed in the adult human brain (Uddin et al., 2008). Moreover, these genes not only show evidence of adaptive evolution on the lineage to the LCA of humans and chimpanzees, but also on both the terminal human and terminal chimpanzee lineages. Considering that mitochondria play an essential central role in the aerobic production of energy, it may be inferred that the adaptive evolution of AEM genes improved the molecular machinery that facilitates the functioning of a high-energy-demanding encephalized brain.

Phylogenomic analysis of approximately 15,000 human coding sequences confirmed that AEM genes were favored targets of positive selection in the ape stem period of human ancestry (i.e., between 25 Mya

and 6 Mya), with 52 AEM genes (cellular component GO:0005739; mitochondrion) in the most enriched cluster of genes showing the signatures of positive selection, that is, faster rate of nonsynonymous substitutions (dN) than synonymous (dS) (Goodman et al., 2009). In the human terminal lineage (from 6 Mya to present), there were also many positively selected AEM genes but not significantly more than expected for any category of genes in the human genome. However, when these analyses were confined to only those positively selected genes that also show brain expression levels equivalent to or greater than the median of all modern human brain-expressed genes (Su et al., 2004), the most enriched clusters in the ape stem and human terminal lineages consisted of 20 and 23 AEM genes, respectively. Of these brain-expressed AEM genes, 14 and 10 in the ape stem and human terminal lineage, respectively, were involved in oxidative phosphorylation (Kyoto Encyclopedia of Genes and Genomes pathway map00190; oxidative phosphorylation). For more detailed information about these data and the methods used to infer enrichment for Gene Ontology terms and Kyoto Encyclopedia of Genes and Genomes pathways, refer to Goodman et al. (2009).

If the evolutionary origins of enlarged hominid brains depended on adaptively evolved AEM genes, then other large-brained mammals should also have in their ancestry AEM genes as principal targets of positive selection. An opportunity to test this hypothesis was provided by the addition of two afrotherian genomes to the growing set of publically available sequenced genomes. These two afrotherian genomes are from a large-brained mammal, the African savanna elephant (*Loxodonta africana*) and a small-brained mammal, the lesser hedgehog tenrec (*Echinops telfairi*). The clade Afrotheria, within which are elephants and tenrecs, is anciently separated from the clade Euarchontoglires, within which are humans and mice (Fig. 3.3*A*). Although elephants and tenrecs are phylogenetically closer to each other than to humans or mice, elephants resemble modern humans by having such features as large brains, empathetic social bonds, high intelligence, and prolonged development and long life spans [Fig. 3.3*B*; as discussed in Goodman et al. (2009)]. In contrast, tenrecs, as insectivoregrade mammals, have small, poorly encephalized brains and short life spans. The phylogenomic patterns of adaptive evolution are more similar between elephant and human than between either elephant and tenrec lineages or human and mouse lineages, with adaptively evolved AEM genes being especially well represented in the elephant and human patterns (Fig. 3.3*C*) (Goodman et al., 2009). In correlation with brain oxygen consumption and brain mass being largest in elephants and next largest in humans, positively selected AEM genes were most evident in the elephant lineage (indeed more overrepresented than any other gene category), next most evident in the human lineage, and not evident (i.e., not overrepresented)




B

| Taxon | Gestation (days) | Life Span (years) | Body Weight (g) | Brain Weight (g) | Encephalization Quotient |
|---|---|---|---|---|---|
| elephant | 660 | 60 | 3505000 | 4420 | 1.6 |
| human | 270 | 75 | 44000 | 1300 | 8.7 |
| tenrec | 46 | 13 | 88 | 0.62 | 0.3 |
| mouse | 20 | 2 | 21 | 0.43 | 0.5 |

FIGURE 3.3 An example of convergent patterns of adaptive evolution in two large-brained taxa (elephants and humans). All data presented and images are adapted from previously published work (Goodman et al., 2009). (*A*) Species phylogeny based on DNA and fossil evidence (Hallström et al., 2007; Murphy et al., 2007; Wildman et al., 2007; Prasad et al., 2008). Lineages of interest are highlighted. (*B*) Life history and phenotype variables among study taxa. Values given are averages. More information and references for these values can be found in Table S1 of Goodman et al. (2009). (*C*) Lineage protein-coding sequence evolution for 501 mitochondria-related genes.

in tenrec and mouse lineages or in the other examined mammalian pair (the two laurasiatherians *Bos taurus* and *Canis familiaris*).

## THE HUMAN BRAIN, DIFFERENT BY DEGREE AND NOT KIND

Darwin's insight that the modern human mind does not differ in kind but rather in degree from other mammalian minds, in our opinion, should serve as the main guidepost for pursuing a phylogenomic search for the genetic roots of the modern human mind. The prospect that high-quality genome sequences will be obtained from thousands of different mammals (Genome 10K Community of Scientists, 2009) promises to make possible such a phylogenomic search. Key to the search will be dense representation of the species and genera in each extant mammalian order. The phylogenetic tree of mammals inferred from genome sequences can then be used to uncover in each evolved lineage the genetic changes that had

occurred between ancestral and descendent genomes. Of particular interest will be those adaptive genetic changes in protein-coding sequences, promoters, and other regulatory sequences.

Phylogenomic research provides an opportunity to identify those parallel or convergent patterns of adaptive genetic evolution that correlate with parallel or convergent patterns of adaptive phenotypic evolution. As an example, brain size increased in parallel in the stem catarrhines and stem platyrrhines (Kay et al., 1997). Encephalization then increased further in ape ancestry, in some Old World monkeys and some New World monkeys (e.g., *Cebus*) (Marino, 1998). In addition to humans, a number of primate species also exhibit a great deal of phenotypic and behavioral plasticity, including chimpanzees, baboons, macaques, and capuchins. Parallel or convergent patterns of adaptive genetic evolution among these species might help elucidate mechanisms contributing to enhanced brain plasticity in modern humans during childhood when the capacity for learning is greatest. Nevertheless, the search for genetic correlates of distinctive human phenotypic features should explore the possibility that some molecular aspects of modern human brain plasticity might be uniquely human. The hypothesis could be tested that adaptive evolution in our recent ancestry increased the diversity of macromolecular specificities involved in neuronal connectivity and neural plasticity. In testing this hypothesis, genes such as those concerned with cell–cell interaction, adhesion, and receptor–ligand binding and their cis-regulatory motifs should be examined. However, we would not be surprised if phylogenomic studies reveal that the genetic underpinnings for the basic mechanisms of brain plasticity are essentially the same as in other catarrhine primates and that the modern human mind differs from the other species primarily because of the modern human brain's larger number of neurons and dendritic connections and much longer periods of postnatal development in a social nurturing environment.

## A MODERN VOYAGE

With the advent of large-scale sequencing technologies and new bioinformatic tools for processing genomic sequence data, we are poised to embark on a new voyage of exploration and inquiry just as Darwin did in 1831. The last decade in particular has seen exponential growth in genome sequence collection and characterization. As we work toward a more complete understanding of genome structure, biology, and evolution, we become better able to develop and test hypotheses concerning a number of fundamental questions in evolutionary biology and human evolution. At the forefront of our interests are those molecular mechanisms and adaptations that have resulted in the modern human mind.

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# 4
# Human Adaptations to Diet, Subsistence, and Ecoregion Are Due to Subtle Shifts in Allele Frequency

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Human populations use a variety of subsistence strategies to exploit an exceptionally broad range of ecoregions and dietary components. These aspects of human environments have changed dramatically during human evolution, giving rise to new selective pressures. To understand the genetic basis of human adaptations, we combine population genetics data with ecological information to detect variants that increased in frequency in response to new selective pressures. Our approach detects SNPs that show concordant differences in allele frequencies across populations with respect to specific aspects of the environment. Genic and especially nonsynonymous SNPs are overrepresented among those most strongly correlated with environmental variables. This provides genome-wide evidence for selection due to changes in ecoregion, diet, and subsistence.

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We find particularly strong signals associated with polar ecoregions, with foraging, and with a diet rich in roots and tubers. Interestingly, several of the strongest signals overlap with those implicated in energy metabolism phenotypes from genome-wide association studies, including SNPs influencing glucose levels and susceptibility to type 2 diabetes. Furthermore, several pathways, including those of starch and sucrose metabolism, are enriched for strong signals of adaptations to a diet rich in roots and tubers, whereas signals associated with polar ecoregions are overrepresented in genes associated with energy metabolism pathways.

Modern humans evolved in Africa approximately 100–200 kya (White et al., 2003), and since then human populations have expanded and diversified to occupy an exceptionally broad range of habitats and to use a variety of subsistence modes. There is wide physiologic and morphologic variation among populations, some of which was undoubtedly shaped by genetic adaptations to local environments. However, identifying the polymorphisms underlying adaptive phenotypes is challenging because current patterns of human genetic variation result not only from selective but also from demographic processes.

Previous studies examined evidence of positive selection by scanning genome-wide SNP data using approaches that are generally agnostic to the underlying selective pressures. These studies detected outliers on the basis of differentiation of allele frequencies between broadly defined populations (Barreiro et al., 2008; Coop et al., 2009), extended regions of haplotype homozygosity (Voight et al., 2006; Wang et al., 2006; Pickrell et al., 2009), frequency spectrum-based statistics (Carlson et al., 2005; Williamson et al., 2007), or some combination of these methods (Sabeti et al., 2007; Jakobsson et al., 2008). These approaches are well suited to detect cases in which selection quickly drove an advantageous allele to high frequency, thereby generating extreme deviations from genome-wide patterns of variation. However, selection acting on polygenic traits may lead to subtle shifts in allele frequency at many loci, with each allele making a small contribution to the phenotype [see Pritchard et al. (2010) for a discussion]. Recent genome-wide association studies (GWAS) support this view in that most traits are associated with many variants with small effects and involve a large number of different loci (Manolio et al., 2009). Given that most phenotypic variation is polygenic, adaptations due to small changes in allele frequencies are likely to be widespread.

Detection of beneficial alleles that evolved under a polygenic selection model may be achieved by an approach that simultaneously considers the spatial distributions of the allele frequencies and the underlying selective pressures. Such an approach was used in the past to identify

several paradigmatic examples of human adaptations. For instance, the similarity between the distributions of endemic malaria and those of the thalassemias and sickle cell anemia led to the hypothesis that disease carriers were at a selective advantage where falciparum malaria was common (Haldane, 1949; Allison, 1954). More recent studies of candidate genes support roles for selection on energy metabolism (Hancock et al., 2008), sodium homeostasis (Thompson et al., 2004; Young et al., 2005), and the ability to digest lactose from milk (Bersaglieri et al., 2004; Tishkoff et al., 2007b) and starch from plants (Perry et al., 2007). Taken together, these examples advance a model whereby exposures to new or intensified selective pressures resulted in physiologic specializations.

Here, we develop and apply an approach that uses information about underlying selective pressures while also controlling for the important effect of population structure in shaping the spatial distribution of beneficial alleles. Our approach allows us to detect subtle but concordant changes in allele frequencies across populations that live in the same geographic region but that differ in terms of ecoregion, main dietary component, or mode of subsistence.

## RESULTS

We used genotype data for 61 human populations, including the 52 populations in the Human Genome Diversity Project Panel (Li et al., 2008), 4 HapMap Phase III populations (Luhya, Maasai, Tuscans, and Gujarati) (www.hapmap.org), and 5 additional populations (Vasekela !Kung sampled in South Africa, lowland Amhara from Ethiopia, Naukan Yup'ik and Maritime Chukchee from Siberia, and Australian Aborigines). For each of these populations, we gathered environmental data for four ecoregion variables (Fig. S1, available online at www.pnas.org/cgi/content/full/0914625107/DCSupplemental) and seven subsistence variables (comprising four subsistence strategies and three main dietary component variables; Fig. S2, available online at www.pnas.org/cgi/content/full/0914625107/DCSupplemental).

For each SNP and each environmental variable, we contrasted allele frequencies between the two sets of populations using a Bayesian linear model method that controls for the covariance of allele frequencies between populations due to population history and accounts for differences in sample sizes among populations. The statistic resulting from this method is a Bayes factor (BF), which is a measure of the support for a model in which a SNP allele frequency distribution is dependent on an environmental variable in addition to population structure, relative to a model in which the allele frequency distribution is dependent on population structure alone. For subsequent analyses, we use a transformed rank

statistic based on the location of each SNP in the overall distribution of BFs. Because we rank each SNP relative to SNPs within the same allele frequency range and from the same ascertainment panel, this transformed rank statistic allows us to make comparisons across SNP sets. To conduct analyses for the two types of variables (ecoregion and subsistence) as a whole, we also calculated for each SNP a minimum rank statistic across all of the variables within each category, which results in a summary statistic for ecoregion and subsistence, respectively.

### Genic and Nonsynonymous SNPs Are Enriched for Signals of Adaptations to Ecoregion and Subsistence

As with any genome-wide scan for selection, there will be SNPs that fall in the extreme tail of the distribution of the test statistic. Therefore, we asked whether two classes of SNPs that are enriched for functional variation [i.e., genic and nonsynonymous (NS) SNPs] are more common in the lower tail of the minimum rank distribution relative to SNPs that are likely to be evolving neutrally (i.e., nongenic SNPs). As shown in Table 4.1, the ratios of the proportions of both genic and NS SNPs to the proportion of nongenic SNPs are significantly greater than 1 across at least two tail cutoffs of the BF distribution (1% and 0.5%) for both variable categories. Importantly, the enrichment of genic and NS SNPs becomes progressively greater in the more extreme parts of the tail. Furthermore, consistent with the fact that a larger fraction of NS SNPs compared with genic SNPs have functional effects, there is a greater enrichment of NS SNPs compared with genic SNPs in the more extreme tail of the distribution. These patterns suggest that the tail of the BF distribution contains true targets of positive selection.

Given that we observed evidence of selection for ecoregion and subsistence overall, we next asked which individual variables may be driving

TABLE 4.1 Proportions of Genic and NS SNPs Relative to the Proportion of Nongenic SNPs in the Tail of the Minimum Rank Distribution

| | Tail Cutoff | | | | | |
|---|---|---|---|---|---|---|
| | Genic:Nongenic | | | NS:Nongenic | | |
| Variable category | 0.05 | 0.01 | 0.005 | 0.05 | 0.01 | 0.005 |
| Ecoregion | 1.06[a] | 1.17[a] | 1.19[a] | 1.20 [a] | 1.58[a] | 1.58[b] |
| Subsistence | 1.04[c] | 1.11[a] | 1.11[b] | 1.12 | 1.60 [a] | 1.87[a] |

[a]Support from >99% of bootstrap replicate.
[b]Support from >97.5% of bootstrap replicate.
[c]Support from >95% of bootstrap replicate.

TABLE 4.2 Proportions of Genic and NS SNPs Relative to the Proportion of Nongenic SNPs in the Tails of the Individual Variable Distributions

| | | Tail Cutoff | | | | | |
|---|---|---|---|---|---|---|---|
| | | Genic:Nongenic | | | NS:Nongenic | | |
| Variable Category | Variable | 0.05 | 0.01 | 0.005 | 0.05 | 0.01 | 0.005 |
| Ecoregion | Dry | 1.06[a] | 1.12[b] | 1.14[b] | 1.18[a] | 1.02 | 1.33 |
| | Polar | 1.05[c] | 1.10[a] | 1.19[a] | 1.19[a] | 1.54[a] | 1.78[a] |
| | Humid temperate | 1.06[a] | 1.11[a] | 1.11[c] | 1.15[a] | 1.14 | 1.17 |
| | Humid tropical | 1.01 | 1.05 | 1.08 | 1.06 | 1.28 | 1.25 |
| Subsistence | Agriculture | 1.01 | 1.03 | 1.04 | 1.03 | 1.32[b] | 1.41[b] |
| | Foraging | 1.03 | 1.04 | 1.04 | 1.25[a] | 1.46[a] | 1.25 |
| | Horticulture | 1.00 | 0.99 | 1.00 | 1.13 | 1.00 | 0.89 |
| | Pastoralism | 1.01 | 1.05 | 1.13[b] | 1.05 | 1.34[c] | 1.33 |
| Main dietary component | Cereals | 1.04 | 1.06 | 1.10 | 1.04 | 1.12 | 1.37[b] |
| | Fats, meat, and milk | 1.03 | 1.09 | 1.07 | 1.13 | 1.14 | 1.29 |
| | Roots and tubers | 1.06[a] | 1.11[a] | 1.13[a] | 1.08 | 1.02 | 1.05 |

[a]Support from >99% of bootstrap replicate.
[b]Support from >97.5% of bootstrap replicate.
[c]Support from >95% of bootstrap replicate.

these signals. To this end, we examined the lower tails of the rank statistic distributions for each individual variable to determine which ones showed the strongest enrichment of genic and NS SNPs. Several ecoregion variables exhibited a significant excess of genic and NS SNPs with low rank statistics, with the strongest signals observed for polar domain (Table 4.2). Fewer individual subsistence variables had strong signals, but two variables are worth noting: the foraging subsistence pattern and roots and tubers as the main dietary component. Fig. 4.1 (Figs. S3-S5, available online at www.pnas.org/cgi/content/full/0914625107/DCSupplemental) illustrates the importance of controlling for population structure to expose these signals, many of which are due to subtle, but consistent, allele frequency shifts across geographic regions. These shifts are detectable even in the face of a large effect of population structure in shaping the geographic distributions of allele frequencies.

Two NS SNPs have extremely high BFs (the highest in their respective frequency bins; *Materials and Methods)* and provide particularly convincing signals of adaptations to dietary specializations. A SNP (rs162036) that is strongly correlated with a diet containing mainly the folate-poor roots

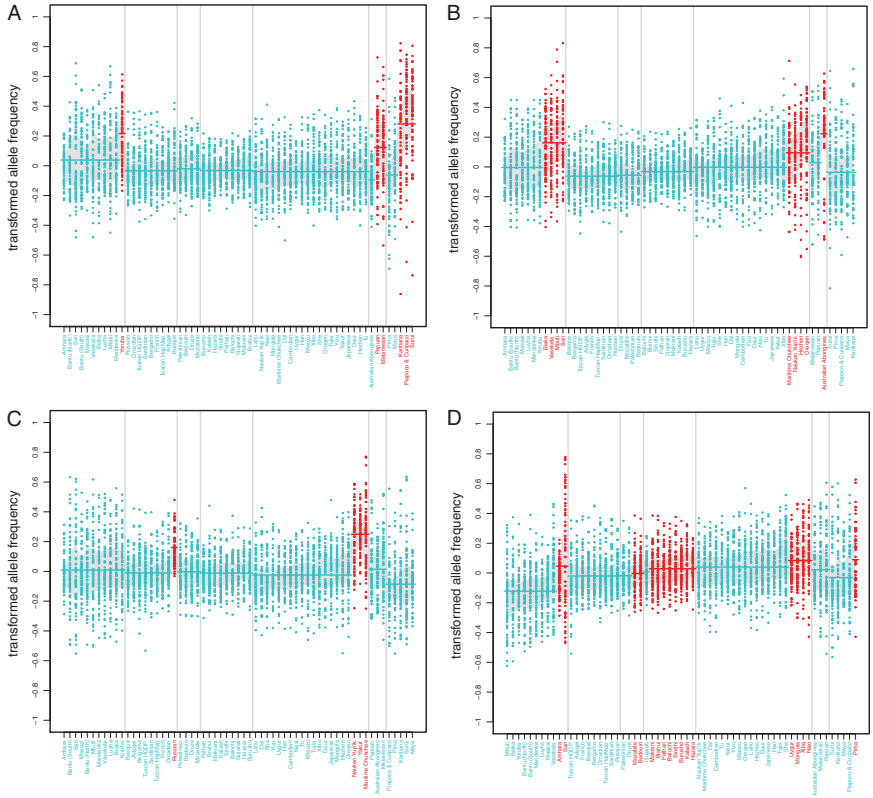


FIGURE 4.1 Transformed allele frequency plotted against population for the variables that showed the strongest enrichment of signal for genic and NS SNPs. Patterns of variation in allele frequencies are shown for *(A)* the main dietary component roots and tubers, (*B*) the subsistence strategy foraging, and for (*C*) polar and (*D*) dry ecoregions. SNPs were polarized according to the relative difference between the two categories in the first region where both were present; then, transformed allele frequencies were computed by subtracting the mean allele frequency across populations. SNPs with rank $<10^{-4}$ are included in the plots. Vertical lines separate populations into one of seven major geographic regions (from left to right: sub-Saharan Africa, Europe, Middle East, West Asia, East Asia, Oceania, and the Americas). Dark gray points denote populations that are members of the dichotomous category, and all other populations are denoted by light gray points. Lines are drawn through the mean for the set of populations in a given region that are part of the category of interest, and gray shading denotes the central 50% interval.

and tubers lies within the methionine synthase reductase *(MTRR)* gene, which activates the folate metabolism enzyme methionine synthase and is implicated in spina bifida (Shaw et al., 2009). Perhaps the most interesting signal comes from a SNP (rs4751995) in pancreatic lipase-related protein 2 *(PLRP2)* that results in premature truncation of the protein and is strongly correlated with the use of cereals as the main dietary component (Fig. 4.2). Several lines of evidence support an important role for this protein in a plant-based diet. First, unlike other pancreatic lipases, PLRP2 hydrolyzes galactolipids, the main triglyceride component in plants (Andersson et al., 1996; Sias et al., 2004). Second, a comparative analysis found that the PLRP2 protein is found in nonruminant herbivore and omnivore pancreases but not in the pancreases of carnivores or ruminants (De Caro et al., 2008). Our results show that the truncated protein is more common in populations that rely primarily on cereals, consistent with the hypothesis that this variant results in a more active enzyme (Lowe, 2002; Berton et al., 2007) and represents an adaptation to a specialized diet.

Previous analyses have used broad-scale population differentiation, measured by $F_{ST}$, to identify loci that show extreme allele frequency differences between populations and, hence, are candidate targets of natural selection. The approach used here is in some ways similar to an $F_{ST}$-based approach, but it differs in several significant regards (see *Discussion).* To assess the importance of these differences, we compared our results with those from a simple $F_{ST}$-based analysis. To this end, we calculated global $F_{ST}$ for each SNP and compared these values with the minimum transformed rank statistics for ecoregion and subsistence. The correlations were extremely low (−0.024 and −0.034 for ecoregion and subsistence,

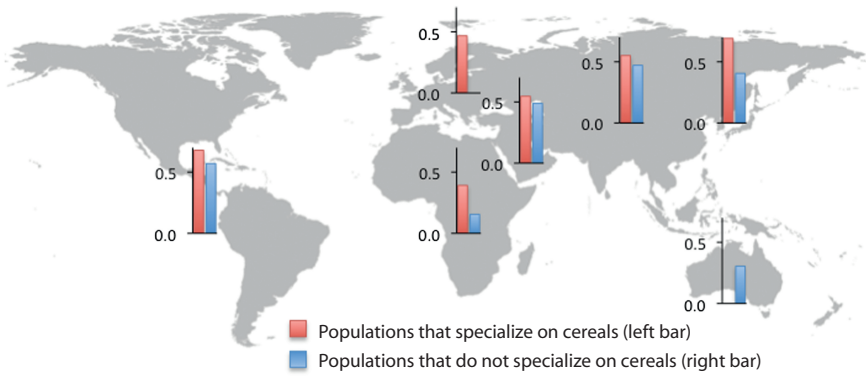


FIGURE 4.2 Average frequencies for PRLP2 W358X (rs4751995) across populations in each major geographic region.

respectively). Further, the amount of overlap in the tails of the distributions (5%, 1%, and 0.5%) was slightly lower than that expected by chance for two independent distributions, suggesting that the environmental contrast approach used here differs from, and is therefore complementary to, a broad-scale $F_{ST}$ approach.

### Clarifying the Biological Relevance of the Strongest Signals

To identify the pathways that were targeted by selection, we asked whether there is an enrichment of signal for particular canonical pathways. Here, we focused on the individual variables with the strongest enrichment of genic relative to nongenic SNPs: roots and tubers as the main dietary component and polar ecoregion. Because we found that proportionally more genic than nongenic SNPs have strong correlations with environmental variables, an enrichment of signals for SNPs in a particular gene set relative to nongenic SNPs could simply reflect this global genic enrichment. Therefore, in this analysis, we examined the tail of the rank statistic distribution and asked whether the proportion of SNPs from genes implicated in a given canonical pathway was greater than the proportion of genic SNPs from all other genes.

The two strongest pathway signals for roots and tubers are with starch and sucrose metabolism and folate biosynthesis (Table 4.3). In light of the fact that roots and tubers are mainly composed of starch and are poor in folates, it is plausible that variation in these pathways is advantageous in populations that rely heavily on these food sources. Among the genes with strong signals in this group, there are several involved in the degradation and synthesis of glycogen *(GAA* and *GBE1).* A gene coding for the cytosolic β-glucosidase *(GBA3)* contains several SNPs strongly correlated with roots and tubers as the main dietary component. This liver enzyme hydrolyzes β-D-glucoside and β-D-galactoside, and it may be involved in the detoxification of plant glycosides, such as those contained in roots and tubers (de Graaf et al., 2001). Several of the pathways with strong signals with polar ecoregion are involved in metabolism (e.g., pyruvate metabolism and glycolysis and gluconeogenesis) (Table 4.3). Among the genes in the pyruvate pathway, we observed particularly strong signals in the gene coding for mitochondrial malic enzyme 3 *(ME3),* which catalyzes the oxidative decarboxylation of malate to pyruvate. Interestingly, the gene coding for another mitochondrial malic enzyme *(ME2)* also contains two SNPs strongly correlated with polar ecoregion. These results suggest a link between cold tolerance and energy metabolism and point to specific variants that are likely to influence cold tolerance. Further, our findings are consistent with a previous study that found strong correlations between variants in genes implicated in energy metabolism and winter temperature

TABLE 4.3 Canonical Pathways Enriched in the 1% and 5% Tails of the Minimum Rank Distribution

| | | | SNPs in Pathway:Other Genic SNPs (tail cutoff) | | |
|---|---|---|---|---|---|
| Variable Category | Variable | Description | 0.05 | 0.01 | 0.005 |
| Ecoregion | Polar domain | Glycolysis and gluconeogenesis | 5.91[a] | 4.86[a] | 2.38[a] |
| | | Bile acid biosynthesis | 7.04[a] | 5.53[a] | 2.61[a] |
| | | Pyruvate metabolism | 6.92[a] | 5.10[a] | 2.72[a] |
| | | 3-Chloroacrylic acid degradation | 17.42[a] | 12.94[a] | 4.22[a] |
| | | Arginine and proline metabolism | 3.42[a] | 3.39[a] | 1.86[a] |
| Subsistence | Roots and tubers | Starch and sucrose metabolism | 2.72[a] | 2.21[a] | 1.61[a] |
| | | Folate biosynthesis | 4.62[a] | 3.65[a] | 2.41[a] |

[a]Support from >99% of bootstrap replicate.

(Hancock et al., 2008) and with studies that show evidence for adaptation in mitochondrial DNA (Ruiz-Pesini et al., 2004; Balloux et al., 2009).

Results of genome-wide association studies with diseases and other complex traits offer an opportunity to connect signals of selection with SNPs influencing specific traits and diseases. To this end, we identified a subset of SNPs with extremely strong correlations with environmental variables that were also strongly associated with traits from 106 GWAS (Table 4.4). We find that several SNPs strongly correlated with subsistence, and main dietary component variables are associated with energy metabolism–related phenotypes [high-density lipoprotein cholesterol, electrocardiographic traits and QT interval (el-Gamal et al., 1995), fasting plasma glucose, and type 2 diabetes]. These signals include a SNP in the type 2 diabetes gene *KCNQ1*, where we find that the risk allele is at higher frequency in populations where cereals are the main dietary component.

## DISCUSSION

This genome-wide scan identified targets of adaptations to diet, mode of subsistence, and ecoregion. The environmental variables in our analysis were chosen to capture the striking diversity among populations in

TABLE 4.4 SNPs with the Strongest Signals of Selection Among Those Associated with Phenotypic Traits in GWAS

| Information About Most Significant Environmental Variable | | | | Disease/Trait Association | | | Genetic Region | |
|---|---|---|---|---|---|---|---|---|
| SNP | Variable Type | Variable | Rank Statistic | Trait | Trait *P* Value | Chr | Position | Nearby Genes |
| rs174570 | Ecoregion | Humid tropical ecoregion | $2.00 \times 10^{-5}$ | LDL<br>Total<br>HDL cholesterol | $4.00 \times 10^{-13}$<br>$2.00 \times 10^{-10}$<br>$4.00 \times 10^{-6}$ | 11 | 61353788 | *FADS2, FADS3* |
| rs2269426 | Subsistence | Fat, meat, milk | $2.44 \times 10^{-5}$ | Plasma eosinophil count | $3.00 \times 10^{-6}$ | 6 | 32184477 | *TNXB, CREBL1* (MHC Class III) |
| rs7395662 | | Foragers | $5.92 \times 10^{-5}$ | HDL cholesterol | $6.00 \times 10^{-11}$ | 11 | 48475469 | *MADD, FOLH1* |
| rs10507380 | | Pastoral | $4.07 \times 10^{-4}$ | Electrocardiographic traits | $8.00 \times 10^{-6}$ | 13 | 26777526 | *RPL21* |
| rs9642880 | | Pastoral | $4.57 \times 10^{-4}$ | Urinary bladder cancer | $9.00 \times 10^{-12}$ | 8 | 128787250 | *MYC, BC042052* |
| rs17779747 | Main dietary component | Roots and tubers | $1.11 \times 10^{-4}$ | QT interval | $6.00 \times 10^{-12}$ | 17 | 66006587 | *KCNJ2* |
| rs2722425 | | Roots and tubers | $2.20 \times 10^{-4}$ | Fasting plasma glucose | $2.00 \times 10^{-8}$ | 8 | 40603396 | *ZMAT4* |
| rs2237892 | | Cereals | $1.49 \times 10^{-4}$ | Type 2 diabetes | $1.70 \times 10^{-42}$ | 11 | 2796327 | *KCNQ1* |

NOTES: Table contains SNPs with an environmental rank less than $5 \times 10^{-4}$ and a GWAS *P* value of less than $1 \times 10^{-5}$. Chr, chromosome; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

ecoregion, diet, and subsistence. Much of this variation is related to major transitions that occurred during human evolutionary history, including the dispersal out of sub-Saharan Africa to regions with different climates and the adoption of more specialized—often less diverse—diets (i.e., farming and animal husbandry vs. foraging). Our results aim to clarify the genetics underlying the adaptive responses to these transitions.

Most human phenotypes, including adaptive traits like height and body proportions, are quantitative and highly polygenic (Manolio et al., 2009), and most human variation is shared across populations. Therefore, the same adaptive allele may often be independently selected in different geographic areas that share the same environment. The environmental aspects considered in this analysis changed dramatically over human evolutionary time. As a result, selection on standing—rather than new—alleles, which afford a faster adaptive response to environmental change (Hermisson and Pennings, 2005), may have played a prominent role in adaptation to new environments. This proposal is supported by expectations of selection models for quantitative traits (Falconer and MacKay, 1996), specifically that selection will generate small allele frequency shifts at many loci until the population reaches a new optimum (Pritchard et al., 2010). Whereas approaches that detect selection under a hard sweep model aim to identify loci that drove a new allele quickly to high frequency in the population (Pritchard et al., 2010), our approach is well suited to detect small shifts in the frequencies of beneficial alleles that have a broad geographic distribution [see Hancock et al. (2010) for a more detailed discussion]. For quantitative traits, the method we use may be particularly appropriate for understanding recent human adaptations. In this sense, our results fill an important gap and are useful for reconstructing the genetic architecture of human adaptations.

Some of our most interesting signals seem to be adaptations to dietary specializations. Although cultural adaptations certainly played an important role in our ability to diversify, there is strong evidence that genetic adaptations have been crucial as well. A previous genome-wide analysis of sequence divergence between species found evidence for ancient adaptations along the human lineage in the promoters of nutrition-related genes along the human lineage (Haygood et al., 2007). Examples of more recent genetic adaptations that were integral for dietary specializations include variants near the lactase gene, which confer the ability for adults to digest fresh milk in agropastoral populations, and an increase in the number of amylase gene copies in horticultural and agricultural populations (Bersaglieri et al., 2004; Perry et al., 2007; Tishkoff et al., 2007b; Enattah et al., 2008). Our results indicate that genetic adaptations to dietary specializations in human populations may be widespread. In particular, we find signals of adaptations in populations that heavily depend on roots and

tubers, which are staple foods in places where cereals and other types of crops do not grow well (e.g., in regions with nutrient-poor soils and with frequent droughts). Given that roots and tubers are rich in carbohydrates, it is particularly compelling that the most significant gene set for populations that depend on this food source is the starch and sucrose metabolism pathway. Further, roots and tubers are low in folic acid, a vitamin with an important role in newborn survival and health; accordingly, we find a strong signal for genes implicated in folic acid biosynthesis in populations that specialize on this food source. Additional signals with diet include those observed in populations that specialize on cereals, with SNPs implicated in type 2 diabetes (Table 4.4) and in the hydrolysis of plant lipids.

Foraging, or hunting and gathering, is the mode of subsistence that characterized human populations since their emergence in Africa until the transition to horticulture, animal farming, and intensive agriculture that occurred starting roughly 10,000 years ago (Smith, 1995). With this transition, many aspects of human ecology dramatically changed, from diet and lifestyle to population densities and pathogen loads. Given that our hominin ancestors were foragers, the signal we observe in the contrast between forager and nonforager populations is likely to reflect adaptations to the less diverse, more specialized diets in horticulture, animal farming, and agriculture (Larsen, 2003). Our findings are consistent with the results of an analysis of the *NAT2* drug metabolizing enzyme gene, which found a significant difference in the frequency of slow acetylator mutations between forager and nonforager (i.e., pastoral and agricultural) populations. These findings were interpreted as the result of the diminished dietary availability of folates consequent to the subsistence and nutritional shift (Luca et al., 2008).

Ecoregion classifications include information about climatic factors, vegetation, geomorphology, and soil characteristics (Bailey and Hogg, 1986). Therefore, they provide an integrated view of many facets of human environments. Interestingly, the strongest signal was observed for the polar domain classification and, to a lesser extent, for the dry and humid temperate domains. Although polar habitats presented diverse challenges to human survival, including cold temperature, low UV radiation, and limited resources, our gene set enrichment analyses suggest that the signals of selection in the polar domain tend to be due to alleles that conferred adaptations to cold stress. In fact, many of the gene sets significantly enriched for signals with the polar domain are directly relevant to energy metabolism and temperature homeostasis. Adaptations in these genes were probably critical in the establishment of stable human populations in the northernmost latitudes of Europe and Asia. Likewise, signals associated with the dry and humid temperate domains may reflect relatively ancient adaptations that occurred during the dispersal of anatomically

modern human populations. The lack of a significant excess of signals associated with the humid tropical domain may be due to a combination of factors, including the fact that humans reentered the humid tropics outside Africa too recently to generate detectable new adaptations.

In some ways our approach is similar to previous analyses based on $F_{ST}$, but there are two important differences. First, we compare populations on the basis of environmental variables rather than their geographic origin, thus providing greater power to detect allele frequency differences that track the underlying selective pressure. Second, unlike other analyses of spatial patterns of variation, we use a test statistic (the BF) that detects a signal relative to a null model that captures aspects of human population structure. Taken together, these two features of our approach allow us to detect novel loci where SNPs show subtle, but consistent, patterns across populations. As a result, our findings differ substantially from the results of previous analyses based on broad-scale population differentiation. The overlap in the tails from global $F_{ST}$ and the minimum ranks for subsistence and ecoregion, respectively, are slightly less than expected by chance.

A possible caveat to the results presented here is that they are due solely to background selection, whereby the elimination of strong deleterious alleles continually arising in genic regions effectively reduces the effective population size of these regions compared to the less constrained nongenic regions. As a result, genic regions may be expected to experience higher rates of genetic drift and to exhibit greater differentiation between subdivided populations compared with neutrally evolving loci (Charlesworth et al., 1997; Hu and He, 2005). Therefore, purifying rather than positive selection could potentially account for the excess of genic SNPs strongly correlated with environmental variables. Although we cannot formally rule out this possibility, we note that two features of our data suggest that background selection does not entirely account for the observed enrichment. One is that the enrichment of genic and NS SNPs becomes more pronounced in the more extreme lower tails of the BF distribution, as expected if at least some of the SNPs were indeed targets of positive selection. The other feature is that the enrichment of NS SNP is quantitatively greater than the enrichment of genic SNPs; because a larger fraction of NS SNPs affect gene function compared with genic SNPs, this is the pattern expected if at least some of the NS SNPs increased in frequency because of a selective advantage.

Our results extend upon and are complementary to results of previous scans for natural selection in humans. By conducting multiple contrasts between populations that differ with respect to ecoregion or subsistence to identify genetic variants that show concordant changes in allele fre-

quencies across populations, we find a set of adaptive SNPs that differs compared with previous analyses that were agnostic to the underlying selective pressure. Further, because the SNPs we identify tend to have a global distribution and to show subtle, but consistent, differences in allele frequencies across populations, loci we identify are likely to represent cases of selection on standing variation. As a result, the findings presented here represent an important step toward clarifying the genetic basis of human adaptations.

## MATERIALS AND METHODS

### Environmental Variables

Ecoregion data were obtained for each population on the basis of coordinates where samples were collected, except for the Vasakela !Kung and the Gujarati, who had recently relocated. For these populations, we used coordinates of their most recent homeland. The individuals who were sampled from the !Kung population were known to have recently relocated to Schmidtsdrift, South Africa, from the Angola/Namibia border, so we used coordinates that reflected their location before this migration. Each population was classified into one of four ecoregion domains, which are defined according to a combination of ecologically important aspects of climate. Therefore, the ecoregion variables are closely related to climate, but they may be a more informative representation of climatic variation. The ecoregion domains comprise polar, humid temperate, humid tropical, and dry. We classified each population on the basis of the coordinates of the population using Bailey's Ecoregion Map (Bailey and Hogg, 1986).

When available, data from Murdock (1967) were used to classify populations according to their main mode of subsistence and dietary specialization. In cases in which Murdock did not have information about a population, we obtained information from the *Encyclopedia of World Cultures* (Levinson, 1991–1996). We classified each population into one of four subsistence categories (foraging, horticultural, agricultural, or pastoral) and into one of three categories based on the main dietary component (cereals; roots and tubers; or fat, meat, or milk). Each population was classified into subsistence and main dietary component categories by two independent researchers, and the small number of discrepancies that were found were resolved by further research. For the five populations that were genotyped by our group, individuals who oversaw collection gave input for classification.

### Detecting Signals Between SNPs and Dichotomous Environmental Variables

To assess evidence for selection related to each dichotomous environmental variable, we contrasted the allele frequencies for each SNP across populations that differ with respect to the environmental variable. More specifically, we used a Bayesian linear model method that controls for population history by incorporating a covariance matrix of populations and accounts for differences in sample size among populations. This method yields a BF that is a measure of the weight of the evidence for a model in which an environmental variable has an effect on the distribution of the variant relative to a model in which the environmental variable has no effect on the distribution of the variant. On the basis of these BFs, for each SNP and each environmental variable, we calculated a transformed rank statistic that was scaled to be between 0 and 1 (with 0 and 1 corresponding to the highest and lowest BF, respectively); this transformed rank statistic is sometimes referred to as an empirical *P* value. Calculating this transformed rank statistic allowed us to control for some aspects of SNP ascertainment and differences in allele frequencies across SNPs. The Illumina 650Y platform used for genotyping is made up of three panels of tagging SNPs that were ascertained in different ways (Eberle et al., 2007). To calculate the transformed rank statistic for each SNP for a given variable, we found the rank of the SNP relative to all other SNPs in the same ascertainment panel and within the same allele frequency bin, where there were 10 allele frequency bins, based on the global derived allele frequency.

To summarize the evidence for selection for each SNP for the two categories of variables (subsistence and ecoregion), we calculated a minimum rank statistic by finding the minimum of the transformed rank statistics across all subsistence and ecoregion variables, respectively. Using these minimum rank statistics, we could ask questions about the evidence of selection for subsistence and for ecoregion overall.

### Assessing the Evidence for an Excess of Functional SNPs in the Tail of the Distribution

To determine whether the lower tail of the rank statistic distribution contains an excess of SNPs enriched for function, compared with that expected by chance, we calculated the proportions of genic and NS SNPs relative to the proportion of nongenic SNPs in the tail. Rather than arbitrarily choosing a single tail cutoff, we examined the enrichment at three tail cutoffs (5%, 1%, and 0.5%). To assess significance for an observed excess, we used a bootstrap resampling technique to obtain confidence intervals on the estimated excess. Because positive selection can result

in increased linkage disequilibrium near a selected variant, we bootstrap resampled across 500-kb segments of the genome. For each of 1,000 bootstrap replicates, we calculated the proportion of genic and NS SNPs relative to the proportion of nongenic SNPs in the tail of the distribution. We consider an excess significant for a given tail cutoff if at least 95% of the bootstrap replicates support an excess of SNPs enriched for function.

### Comparison of Results from Environmental Contrasts and $F_{ST}$

We calculated global $F_{ST}$ values (Weir and Cockerham, 1984) for the complete set of 61 populations. Then, for each SNP, we calculated a transformed rank statistic as we had done for the environmental variable contrasts. Next, we calculated Spearman correlation coefficients between $F_{ST}$ values and the minimum transformed rank statistic from the environmental contrast analyses. In addition, we assessed the amount of overlap in the tails of the distributions for $F_{ST}$ and environmental contrasts relative to chance.

### Canonical Pathway Analysis

To determine whether there was an enrichment of signal for a particular canonical pathway, we used a method similar to that used to test for an excess of genic and NS SNPs relative to nongenic SNPs in the tails of the test statistic distribution. Here, we compared the proportion of SNPs from a given pathway with the proportion of all other genic SNPs in the tail of the minimum rank distribution and of the transformed rank distributions for the individual variables with the strongest genic enrichment. To assess significance for the findings and to ensure that the results are not driven by one or a few genomic regions, we applied the same bootstrap approach described above. The lists of genes included in each of the 438 canonical pathways were obtained from the Molecular Signatures Database (Subramanian et al., 2005).

### Comparison with GWAS Results

We downloaded the Catalog of Published Genome-Wide Association Studies (Hindorff et al., 2009) on July 14, 2009, which includes information about SNPs with reported associations with $P < 1 \times 10^{-5}$. We filtered this database for SNPs found on the Illumina HumanHap650Y platform; there were entries for 800 unique autosomal SNPs implicated in 61 traits. From among these SNPs, we identified a set of SNPs with extremely low rank statistics ($<5 \times 10^{-4}$) for each of the subsistence and ecoregion variables. Given that most GWAS are performed in populations of European ances-

try, we binned the SNPs in the Illumina panel on the basis of the allele frequency in Europeans rather than the global allele frequency to calculate the transformed rank statistics.

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# 5
# Working Toward a Synthesis of Archaeological, Linguistic, and Genetic Data for Inferring African Population History

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Although Africa is the origin of modern humans, the pattern and distribution of genetic variation and correlations with cultural and linguistic diversity in Africa have been understudied. Recent advances in genomic technology, however, have led to genome-wide studies of African samples. In this chapter, we discuss genetic variation in African populations contextualized with what is known about archaeological and linguistic variation. What emerges from this review is the importance of using independent lines of evidence in the interpretation of genetic and genomic data in the reconstruction of past population histories.

Disentangling past population histories is a formidably complicated task that benefits from the synthesis of archaeological, linguistic, and genetic data. Archaeology permits insights into ancient technology and culture and provides a timetable for the emergence of innovations. Historical linguistic data complement the archaeological record by contributing an independent phylogenetic analysis of language relationships and providing clues about ancient population migration and admixture events. Similarly, genetic data provide an independent data source to understand the biological relationships among modern peoples

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and likely points of origin and expansion of their ancestors. Undoubtedly, the specific details of human demographic history are more complex than any synthesis can account for, but we are focusing here on the overlap among the archaeological, linguistic, and genetic data collected in Africa to make inferences about African demographic history.

## AFRICAN LANGUAGE FAMILY CLASSIFICATION

Africa is home to almost a third of all modern languages, encompassing >2,000 ethno-linguistic groups (Tishkoff et al., 2009) that have largely been classified into four language families: Niger-Kordofanian, Afroasiatic, Nilo-Saharan, and Khoesan. As displayed in Fig. 5.1, Niger-Kordofanian languages are spoken throughout western Africa, eastern Africa, central Africa, and southern Africa and include the common Bantu languages. The Afroasiatic language family includes languages spoken in northern, central, and eastern Africa such as Cushitic, Chadic, Semitic, and ancient Egyptian. The Nilo-Saharan language family is spoken predominantly in central and eastern Africa and includes the Sudanic and Nilotic languages. The Khoesan language family, which includes languages that

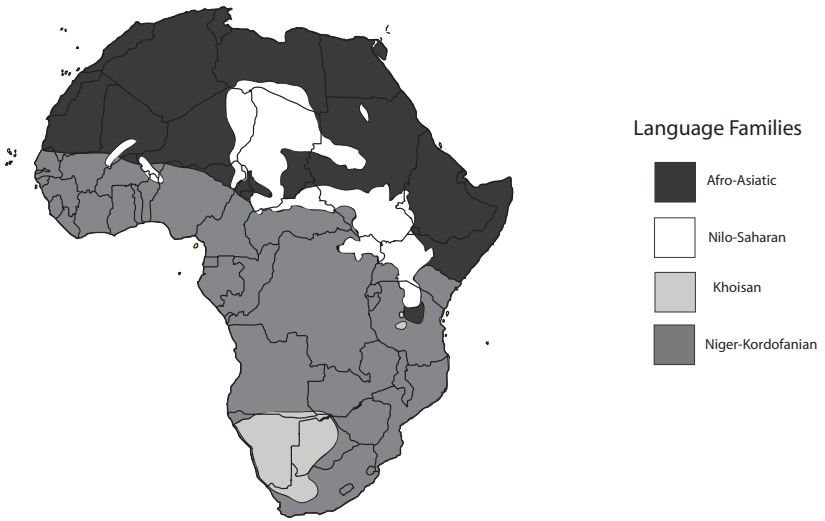


FIGURE 5.1 Map of Africa colored by the language family spoken in each region [adapted from Campbell and Tishkoff (2008)]. The Afroasiatic language family is shown in dark gray, the Nilo-Saharan language family is shown in white, the Khoesan language family is shown in light gray, and the Niger-Kordofanian language family is shown in medium gray.

contain click consonants and is spoken by hunter-gatherer populations in eastern (Hadza and Sandawe) and southern Africa [the San, referred to here as "southern African Khoesan" ("SAK")], is the most contentious of the African language families because there is so much divergence among the Hadza, Sandawe, and SAK languages (Nurse, 1997; Sands, 1998).

## MODERN HUMAN ORIGINS AND MIGRATION OUT OF AFRICA

The earliest emergence of anatomically modern humans in the fossil record occurred in eastern Africa 200–150 thousand years ago (kya) (McDermott et al., 1996; J.D. Clark et al., 2003; McDougall et al., 2005; Trinkaus, 2005). Although the earliest dated modern humans outside of Africa were identified in the Middle East ~90 kya (Schwarcz et al., 1988; Stringer et al., 1989; McDermott et al., 1993; Mercier et al., 1993; Trinkaus, 2005), there was no continuous occupation of regions outside of Africa until ~60–40 kya; modern human remains are documented in Papua New Guinea 60–40 kya (Groube et al., 1986), southwest Asia ~35 kya, Europe ~40 kya, and mainland Asia ~35 kya (Trinkaus, 2005). Therefore, over half of modern human history took place within Africa exclusively, and understanding patterns of variation within Africa is critical for the elucidation of modern human demographic history.

Genetic data from extant modern humans complement the fossil record in the reconstruction of modern human origins. The uniparentally inherited mitochondrial DNA (mtDNA) and nonrecombinant portion of the Y chromosome (NRY) are two loci that have been extensively studied in human populations, in part because they represent the maternal and paternal population histories, respectively, in a population sample and in part because they do not undergo recombination and, therefore, lineages can be more easily traced back to a single common ancestor. Unfortunately, the mtDNA and NRY loci are single loci, which are susceptible to the effects of natural selection and genetic drift because they have smaller effective population sizes relative to the autosomes and because any selective pressure will impact the entire locus. Thus, combined mtDNA, NRY, and autosomal data are necessary for a thorough understanding of any population history.

The mtDNA, NRY, and autosomal DNA studies demonstrate that the highest levels of genetic variation are present in African samples relative to non-Africans, consistent with a model of African ancestry for all modern humans [e.g., Cann et al. (1987), Underhill et al. (2001), International HapMap Consortium (2003), Akey et al. (2004); Frazer et al. (2007), Garrigan et al. (2007), Li et al. (2008), Tishkoff et al. (2009)]. Further, phylogenetic analysis of mtDNA and NRY variation reveals that the deepest phylogenetic clades are found exclusively in African samples and all

non-African lineages derive from a subset of these African lineages (Cann et al., 1987; Ingman et al., 2000; Underhill et al., 2001; Gonder et al., 2007; Tishkoff et al., 2007a; Behar et al., 2008; Henn et al., 2008). Consistent with the archaeological record, estimates of the time to the most recent ancestor (TMRCA) for the mtDNA lineages give an age range of ~200–100 kya (Ingman et al., 2000; Salas et al., 2002; Tang et al., 2002; Behar et al., 2008) and similar results have been published for NRY lineages, ~200–65 kya (Scozzari et al., 1999; Underhill et al., 2000; Tang et al., 2002). Therefore, the genetic data corroborate a model in which modern humans arose in Africa 200–100 kya and subsequently, one or more populations split off and migrated out of Africa. The migration out of Africa was accompanied by a population bottleneck, which resulted in a reduction in genetic diversity in non-African populations relative to Africans (Campbell and Tishkoff, 2008).

## MIDDLE STONE AGE IN AFRICA

The Middle Stone Age, which took place ~250–40 kya (Henshilwood et al., 2002), is a period in the archaeological record that indicates a significant change in culture and subsistence technology in Africa. Several sites in eastern, central, and southern Africa contain artifacts consistent with a shift in technology and population expansion ~75–55 kya, including hunting weapons, indications of increased plant utilization, signs of increased marine exploitation, and evidence of large-scale movement of red ochre (used for art), stone, and shell ornaments (McBrearty and Brooks, 2000; Henshilwood et al., 2001, 2002; Mellars, 2006). It is tempting to speculate that these developments are tied to improvements in human communication; however, the reconstruction of proto-languages does not extend back this far in time; therefore, there is no empirical way to establish when or where human language emerged. Interestingly, an analysis of mtDNA data estimates a population expansion in Africa 70 kya (Excoffier and Schneider, 1999), consistent with the archaeological evidence from the late Middle Stone Age. Furthermore, we would not expect to see the same signal of expansion in non-African populations given that the extreme bottleneck associated with the migration out of Africa most likely obscures more ancient demographic signals.

## NEOLITHIC IN AFRICA

The Neolithic period, beginning ~10 kya, included the development of agriculture and animal domestication in Africa, with concomitant changes in population demographics due to population growth and migration to new regions. Below we discuss several such movements including

the spread of agriculture, the spread of pastoralism, and the dispersal of affiliated language groups and genetic lineages. It is important to note, however, that these associations among linguistic, archaeological, and genetic data are not presented here to paint a simple picture of migration or replacement, but rather to illustrate that large-scale movements of technology and culture have resulted in detectable amounts of gene flow among the involved peoples and that the interpretation of extant genetic patterns benefits from an understanding of the combined data.

**Neolithic in Northern Africa**

Approximately 14 kya, climatic changes associated with the end of the Last Glacial Maximum resulted in regions around the world becoming more favorable to human exploitation. Northern Africa is one such region, and ~13 kya, novel technologies ("Natufian") thought to be the immediate precursor to agricultural technologies emerged and were associated with semisedentary subsistence and population expansions in northeastern Africa (Bar-Yosef, 1987). Moreover, before the emergence of the Natufian-styled artifacts, the archaeological record includes two artifact styles, the "Geometric Kebaran" and the "Mushabian" associated with Middle Eastern and Northern African populations, respectively (Bar-Yosef, 1987). The archaeological evidence suggests the peoples using these assemblages interacted for well over 1,000 years, and linguistic evidence suggests that the peoples using these assemblages may have spoken some form of proto-Afroasiatic (Bar-Yosef, 1987; Ehret et al., 2004). Although the origins of the Afroasiatic language family remain contentious, linguistic data generally support a model in which the Afroasiatic language family arose in Northern Africa >10 kya (Ehret et al., 2004). Moreover, analyses of the Cushitic branch of the Afroasiatic language family suggest that proto-Cushitic arose and diversified at least 7 kya, and this likely took place in Ethiopia (Ehret, 1979).

Intriguingly, the origin and diversification of proto-Afroasiatic is consistent with the spread of intensive plant collection in the archaeological record, and some interpret this pattern to represent a model in which proto-Afroasiatic speakers developed the novel subsistence technology resulting in the expansion and spread of their Afroasiatic descendants in the region (Ehret, 1979). Some examples of the relevant linguistic data include reconstructed Chadic root words for "porridge" and "sorghum" and the Cushitic root words for "grain" and "wheat" (Ehret, 1979). Because these and other root words are present in many of the Chadic and Cushitic languages, it is assumed that they were present in the proto-Chadic and proto-Cushitic languages and therefore must be as old as those proto-languages (Ehret, 1979).

The genetic data appear to be consistent with the archaeological and linguistic data indicative of extensive population interactions between North African and Middle Eastern populations. A recent NRY study explores the distribution of haplogroups in a sample of African, Middle Eastern, and European males (Semino et al., 2004). Whereas a subclade of haplogroup E (M35) appears to have arisen in eastern Africa over 20 kya and subsequently spread to the Middle East and Europe, haplogroup J (M267) appears to have arisen in the Middle East over 20 kya and subsequently spread into northern Africa (Semino et al., 2004). A recent study of genome-wide autosomal microsatellite markers reports that Middle Eastern and African samples share the highest number of alleles that are also absent in other non-African samples, consistent with bidirectional gene flow (Tishkoff et al., 2009). In addition, a recent study of domestic goat mtDNA and NRY variation reports similar findings as well as evidence of trade along the Strait of Gibraltar (Pereira et al., 2009). The combined archaeological, linguistic, and genetic data, therefore, suggest bidirectional migration of peoples between northern Africa and the Levant for at least the past ~14 ky.

**Neolithic in Sahel**

There is increasing archaeological, linguistic, and genetic evidence that the Sahel has been an important region for bidirectional migration between western and eastern Africa (Bereir et al., 2007; Cerny et al., 2007; Hassan et al., 2008; Tishkoff et al., 2009). Linguistic evidence indicates population interactions for ~20–10 kya between the Nilo-Saharan and Afroasiatic speakers in this region (Cavalli-Sforza et al., 1994). The combined linguistic and archaeological data support a model in which the Nilo-Saharan language family arose in eastern Sudan >10 kya and Nilo-Saharan speakers subsequently migrated westward to Lake Chad and southward into southern Sudan (Ehret, 1983; Tishkoff et al., 2009). Linguistic data also suggest that ~7 kya, proto-Chadic Afroasiatic speakers migrated from the Sahara into the Lake Chad Basin (Newman, 1997). This possibility is supported by an analysis of NRY variation that finds that the pattern and distribution of haplogroup R (V88) are consistent with the emergence of proto-Chadic ~7 kya and subsequent expansion of this linguistic group into the Lake Chad Basin (Cruciani et al., 2010). Whereas the inferred migration route is not consistent between NRY and mtDNA analyses, perhaps due to sex-biased migration, studies of mtDNA corroborate a model in which Sahel is a corridor for bidirectional migration between eastern and western Africa and, on the basis of the distribution of haplogroup L3f3, the proto-Chadic speakers expanded from eastern Africa into the Lake Chad Basin (Cerny et al., 2007, 2009).

**The Spread of Pastoralism**

Archaeological data suggest that the emergence of animal husbandry in northeastern Africa took place as early as ~11 kya (Wendorf and Schild, 1998). Archaeological studies in Nabta Playa (in Egypt's Western Desert) reveal a spectrum of artifacts consistent with pastoralism and adaptation to the desert environment, including particular pottery styles (Khartoum tradition), evidence of well technology, and cattle burials (McDonald, 1998; Wendorf and Schild, 1998). By ~8 kya, evidence is present of imported (from the Middle East) sheep or goat remains in northeastern Africa [e.g., McDonald (1998)]. Some controversy persists in the archaeological community regarding whether cattle domestication was developed in northern Africa or imported from the Middle East; however, recent DNA analysis of extant indigenous African bovine taurine and zebu cattle (Hanotte et al., 2002) supports a model in which the earliest emergence of pastoralism involving taurine cattle took place in northeastern Africa and subsequently spread westward and southward (Hanotte et al., 2002). A recent analysis of NRY variation in 13 eastern and southern African population samples suggests that the spread of pastoralism from eastern Africa to southern Africa was accompanied by migration of pastoral peoples as well as pastoral technology as evidenced by the distribution of NRY haplogroup M293 (and the subclade E3b1f-M293) (Henn et al., 2008). Furthermore, the most likely source for this migration based on the samples included in Henn et al. (2008) would have been the southern Nilotic speaking Datog (because the haplotype frequency and diversity of M293 is highest in the Datog) ~2 kya (Henn et al., 2008).

Ehret (1967) inferred the history of pastoralism in Africa from a linguistic analysis of shared cognates. His findings support a relatively ancient emergence of pastoralism in northeastern Africa corresponding to Eastern Sudanic, Central Sudanic, and possibly Southern Cushitic speakers, followed by the subsequent spread of cattle keeping to western and southern Africa (Ehret, 1967). The relatively ancient emergence of pastoralism in the archeological record is supported by the reconstruction of proto-Cushitic languages. For example, there are at least two words for cattle that are thought to be relatively old, one in Northern Cushitic and the other in Central Cushitic. In proto-Cushitic, the word "hlee," which translates to "head of cattle," is related to the Southern Cushitic (Mbugu) word "hline," which translates to "heifer" (Ehret, 1967), and so on. Furthermore, estimates of linguistic diversity of vocabulary related to cattle suggest that cattle keeping arose in northeastern Africa and subsequently spread to western and southern Africa (Ehret, 1967).

Ehret (1967) also argues that the spread of cattle milking was separate and more recent than the spread of cattle keeping. He discusses the assumption that the spread of cattle milking would require some discern-

ible impact on the language used to discuss it (Ehret, 1967). For example, the proto-Bantu word for milk is related to the proto-Bantu word for breast, but there are several root words for milk (many likely borrowed from other languages) among the Bantu languages. However, there is only one root word for milking (literally to squeeze). This observation is interpreted to support a model in which a Bantu population in Tanzania borrowed the word (possibly from the southern Cushitic speakers) representing milking as well as the actual technology related to cattle milking and subsequently spread the technology to other Bantu-speaking populations (Ehret, 1967).

The shift from food gathering to food producing inferred from African archaeological and linguistic data also resulted in a detectible genetic signal. This relationship between subsistence, culture, and biology due to gene/culture coevolution is one that has been of special interest in human genetics studies. Models of Darwinian (i.e., positive) selection are consistent with subsistence being an environmental factor that can have a profound effect on patterns of genetic variation, and the emergence of agriculture and pastoralism is tied to increased population densities and dietary changes. Thus, genetic variants that conveyed a selective advantage in this shift in diet from foraging to animal and plant products would have persisted and increased in frequency in agricultural and pastoralist communities.

Lactase persistence is one of the better studied examples of gene/culture coevolution (e.g., Durham, 1991; Hollox and Swallow, 2002). In most mammals, once an individual is weaned, it loses the ability to produce the enzyme lactase-phlorizin hydrolase (LPH), which is necessary to digest the sugar lactose present in milk without gastric distress (Ingram et al., 2009). The majority of humans do not express this enzyme as adults (referred to as the "lactase nonpersistence" phenotype) (Swallow, 2003). Several widespread mutations, however, result in the continued production of LPH into adulthood, a trait often referred to as lactase persistence (Tishkoff et al., 2007b). The distribution of the lactase persistence phenotype is intriguing given what is known about subsistence patterns worldwide (Fig. 5.2). Lactase persistence is present at high frequency in Northern European dairying and African pastoralist populations; at moderate frequency in southern European and Middle Eastern populations; and at low frequency in nonpastoral Asian, Pacific, American, and African populations (Ingram et al., 2009). In Europeans, the most common mutation associated with lactase persistence is thought to be a regulatory mutation located upstream of the gene that encodes LPH (a T at position –13910), within intron 13 of the neighboring *MCM6* gene (Enattah et al., 2002; Swallow, 2003). Further, this mutation is located within a large linkage disequilibrium block that is thought to have arisen ~20–2 kya, consistent

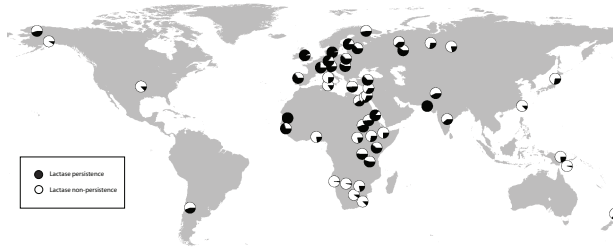


FIGURE 5.2 Global map showing the frequency of the lactase persistence trait for populations reported in Ingram et al. (2009) and citations therein. Lactase persistence is shaded in black.

with recent positive selection related to the emergence of cattle domestication and milk consumption ~10 kya in the Middle East (Edwards et al., 2007; Enattah et al., 2008).

In African populations, the lactase persistence phenotype is generally highest in pastoral populations (Swallow, 2003; Mulcare et al., 2004; Ingram et al., 2007, 2009; Tishkoff et al., 2007b). However, with the exception of the Fulani and Hausa populations (Mulcare et al., 2004), other African pastoralist populations do not have the T-13910 mutation associated with the lactase persistence trait (Ingram et al., 2007; Tishkoff et al., 2007b). Recent studies have identified at least three additional and independent mutations that are associated with lactase persistence in East African pastoralist populations: C-14010, which is most common in Kenya and Tanzania (Tishkoff et al., 2007b); G-13907, which is present at low to moderate frequency in northeast Africa (Ingram et al., 2007; Tishkoff et al., 2007b); and G-13915, which is most common in the Middle East (Enattah et al., 2008) and northeastern Africa (Ingram et al., 2007; Tishkoff et al., 2007b) and may be associated with camel domestication in the Middle East ~6 kya (Enattah et al., 2008). Tishkoff et al. (2007b) demonstrated that all three variants result in significant increases in gene expression levels driven by the lactase promoter.

The most common variant within Africa associated with lactase persistence (C-14010) is also located within an extremely large linkage disequilibrium block (2 Mb) and is thought to have arisen ~6.8–2.7 kya in either the agropastoralist Afroasiatic populations that migrated into Kenya and Tanzania from Ethiopia within the past 5,000 years or the Nilo-Saharan pastoralist populations that migrated into the region from southern Sudan within the past 3,000 years, and the variant then subsequently spread throughout pastoral populations in eastern Africa relatively rapidly, con-

sistent with the spread of pastoralism into sub-Saharan Africa ~4.5 kya (Tishkoff et al., 2007b). The estimates of the selection coefficients of the African mutations (0.035–0.097) are among the highest reported for modern humans, and intuitively this makes sense given not only the increased nutritional value of drinking milk as an adult but also the increased source of water in regions such as the Sahara where dehydration and diarrhea can cause death.

**Bantu Expansion**

In sub-Saharan Africa, the long-range exchange networks of Neolithic technology and associated spread of Bantu languages (which we refer to here as the "Bantu expansion" for the sake of simplicity) have had a major influence on biological and cultural diversity in sub-Saharan Africa. On the basis of archaeological and linguistic data, the Bantu languages and associated agricultural and iron age technologies are thought to have originated in Nigeria or Cameroon (Greenberg, 1972) ~5,000 years ago (Phillipson, 1975; Berniell-Lee et al., 2009) and spread relatively rapidly across sub-Saharan Africa. The extent to which this was associated with the migration of populations vs. a diffusion of language and technology among populations has been debated.

The linguistic classification of the ~600 Bantu languages is interpreted to represent several dispersals throughout sub-Saharan Africa [e.g., Vansina (1995)]. Ehret (2001) argues that proto-Bantu diverged into several daughter clades, all but one of which are spoken only in the northwestern region of the Bantu-speaking areas (i.e., western central Africa), and the other of which was a forest Savanna Bantu clade. Ehret (2001) goes on to argue that the forest Savanna Bantu clade diverged into several daughter clades, including the Savanna Bantu clade, and this diversification is linked to the spread of Bantu languages into central and southern Africa. The Savanna Bantu clade includes most of the contemporary languages spoken in eastern Africa, southeastern Africa, southwestern Africa, and the southern Savanna belt. This reconstruction supports a model in which proto-Bantu emerged in western central Africa ~5,000 years ago and diversified and spread across the rainforest for ~2,000 years before the first archaeological evidence of eastern Bantu speakers in the Great Lakes region (Ehret, 2001).

Archaeological evidence related to the Bantu expansion largely focuses on the distribution of Early and Late Iron Age sites in Africa. Phillipson argues that the Eastern Bantu languages likely arose in western central Africa around the time of the emergence of Early Iron Age artifacts consistent with cattle keeping, but that the spread of Eastern Bantu languages

is associated with the distribution of "later Iron Age" sites in central and southern Africa (Phillipson, 1976).

There is also a genetic signature of past population movements thought to be associated with the Bantu expansion. The large majority of genetic analyses have focused on mtDNA and NRY data. Overall, both datasets tie particular mtDNA (e.g., L0a, L2a, L3b, and L3e) (Pereira et al., 2001; Salas et al., 2002, Plaza et al., 2004; Beleza et al., 2005; Wood et al., 2005; Quintana-Murci et al., 2008) and NRY [e.g., E3a (M2/M180), E2 (M75), and B2a (M150)] (Beleza et al., 2005; Henn et al., 2008; Berniell-Lee et al., 2009) lineages to the Bantu expansion, because they are found in the highest frequencies in extant Bantu-speaking populations. Interestingly, comparative studies of mtDNA and NRY variation suggest different maternal and paternal population histories related to the Bantu expansion (Beleza et al., 2005; Wood et al., 2005). Specifically, NRY variation in regions affected by the Bantu expansion is low relative to mtDNA variation and consists almost exclusively of haplogroup lineages associated with the Bantu expansion (Wood et al., 2005). Conversely, the mtDNA haplogroup lineages in the same samples include lineages associated with the Bantu expansion as well as lineages that are thought to have been present in the region before the Bantu expansion (Tishkoff et al., 2007a). This discrepancy is largely attributed to sex-biased migration and gene flow due to the practice of patrilocality and/or polygyny (Wood et al., 2005; Pilkington et al., 2008), both of which are common in present-day Bantu-speaking populations. Moreover, this pattern of sex-biased gene flow is documented independently in other regions of the world such as the Pacific Islands (Scheinfeldt et al., 2006; Friedlaender et al., 2008). Both loci, however, are more susceptible to genetic drift than autosomal loci because of their relatively smaller effective population sizes; therefore, some of the differential male/female patterns may be attributed to chance. A recent analysis of genome-wide autosomal data is consistent with a large genetic impact of the Bantu expansion on most of sub-Saharan Africa, as evidenced by the presence of Niger-Kordofanian ancestry in many central, eastern, and southern African populations (Tishkoff et al., 2009). In addition, Tishkoff et al. (2009) documented evidence from their analysis of genome-wide autosomal loci of a distinct Bantu migration from eastern to southern Africa, which is consistent with the archaeological and linguistic evidence of dispersal of Bantu technology and languages from the Great Lakes region of East Africa (Ehret, 2001).

## CONTEMPORARY AFRICAN GENETIC AND LINGUISTIC VARIATION

Scholars have studied language relationships within a cladistic framework since at least the early 19th century (Atkinson and Gray, 2005), and given the parallels in linguistic and genetic change over time, it is not unreasonable to use linguistic affiliations as a way of grouping individuals for genetic study. Several studies have demonstrated a correlation between linguistic and genetic variation, including cases in Europe (Cavalli-Sforza and Feldman, 1981; Piazza et al., 1995), Asia (Karafet et al., 2001), the Pacific (Merriwether et al., 1999; Robledo et al., 2003; Scheinfeldt et al., 2006; Friedlaender et al., 2008), and the Americas (Smith et al., 2000; Malhi et al., 2001; Eshleman et al., 2004; Wang et al., 2007). The main difficulty in these studies lies in the interpretation of linguistic similarities among populations. Whereas language sharing obviously results from some degree of contact among peoples, the horizontal transmission of language can occur with little to no genetic exchange. Likewise, there can be genetic exchange with little or no linguistic exchange. Therefore, the degree of correlation between genetic and linguistic variation varies depending on the populations being studied.

Studies of genetic variation within Africa, as mentioned above, have found extensive amounts of genetic variation relative to non-Africans owing to the fact that the "out of Africa" bottleneck significantly reduced genetic variation in non-Africans; however, most genetic studies of African populations are limited by the number of population samples included. More recent work has improved the understanding of genetic variation in Africa with a survey of genome-wide genetic variation in geographically and ethnically diverse African samples (Tishkoff et al., 2009). Tishkoff et al. (2008) analyzed 1,327 genome-wide autosomal microsatellite and insertion/deletion polymorphisms in 121 African population samples and a comparative sample of 1,394 non-Africans. The authors (Tishkoff et al., 2009) studied population structure and relationships using the program STRUCTURE (Pritchard et al., 2000), among other phylogenetic analyses. The STRUCTURE program uses a model-based Bayesian clustering approach to identify genetic subpopulations and assign individuals probabilistically to these subpopulations on the basis of their genotypes, while simultaneously estimating ancestral population allele frequencies. The program STRUCTURE places individuals into $K$ clusters, where $K$ is chosen in advance and is varied across independent runs, and individuals can have membership in multiple clusters (Pritchard et al., 2000). Tishkoff et al. (2009) inferred 14 ancestral population clusters globally as well as within Africa and found that the African samples cluster geographically as well as linguistically and ethnically (Table 5.1). In addition to the STRUCTURE analysis, the authors (Tishkoff et al., 2009) constructed a

TABLE 5.1 Inferred Population Clusters Using the STRUCTURE Analysis of Autosomal Microsatellite and Insertion/Deletion Polymorphism Data from Global Populations Adapted from Tishkoff et al. (2009)

| *K* | Emerging Clusters |
|---|---|
| 2 | African, non-African |
| 3 | East Asian, Oceanic, Native American |
| 4 | Eastern African |
| 5 | Hadza, Sandawe, SAK, Pygmy |
| 6 | Western Pygmy |
| 7 | Chadic, Nilo-Saharan |
| 8 | Indian, Oceanic |
| 9 | Oceanic |
| 10 | Native American |
| 11 | Mbuti Pygmy, SAK |
| 12 | Chadic/Nilo-Saharan speakers from northern Cameroon, Chad, and southern Sudan |
| 13 | Sandawe |
| 14 | Fulani |

neighbor-joining tree on the basis of pairwise population genetic distances that showed that the African samples clustered primarily by geographic region and to a lesser extent by linguistic affiliation with a few notable exceptions. The pygmies from central Africa, for example, clustered near the southern African San.

Several studies have looked at the relationship between genetic and linguistic variation in African samples (Sanchez-Mazas, 2001; Lane et al., 2002; Tishkoff et al., 2007a, 2009; Hassan et al., 2008; Henn et al., 2008; Bryc et al., 2010). For example, an NRY study of Nilo-Saharan, Niger-Congo, and Afroasiatic speakers in Sudan revealed a strong correlation (Mantel test: $r = 0.31$, $P = 0.007$) between linguistic and NRY variation (Hassan et al., 2008), and in this case the correlation between linguistic and genetic variation was stronger than the correlation between geographic and genetic distances (Mantel test: $r = 0.29$, $P = 0.025$). Similarly, a study of mtDNA and NRY variation in 40 African samples representing all four language families reports a significant correlation between genetic and linguistic distances (Mantel of NRY, $r = 0.32$, $P = 0.001$; Mantel of mtDNA, $r = 0.23$, $P = 0.016$) (Wood et al., 2005).

The single-locus studies of genetic and linguistic correlation are consistent with the regression analysis reported by Tishkoff et al. (2009) that documents significant correlations between linguistic and genetic distances

within the Niger-Kordofanian and Nilo-Saharan language families after correction for geographic distances. To further explore the relationship among genetic and linguistic variation in Africa, we used the published dataset of genome-wide data from Tishkoff et al. (2009) that includes 103 population samples ($n \geq 10$) that speak languages representing all four African language families. We first performed a Mantel test to determine to what extent genetic and linguistic distances are correlated within language families. Not surprisingly, all three tests showed that linguistic and genetic distances were significantly correlated (with 100,000 permutations): Niger-Kordofanian, $r = 0.32$, $P = 9.99^{-6}$; Nilo-Saharan, $r = 0.29$, $P = 9.99^{-6}$; and Afroasiatic, $r = 0.27$, $P = 9.99^{-6}$ (the linguistic relationships among the Khoesan speakers are not clearly understood and therefore did not permit the construction of a linguistic distance matrix needed to perform a Mantel test); and the correlation coefficient is >25% in all three tests.

Because we and others (Tishkoff et al., 2009) have established a significant correlation between linguistic affiliation and genetic variation within three of the African language families, we wanted to explore to what degree samples plotted by genetic distance cluster by language family. We used multidimensional scaling (MDS) to construct a two-dimensional plot of a pairwise genetic distance matrix taken from the above-mentioned 103 population samples (Tishkoff et al., 2009). Consistent with the mtDNA and NRY studies discussed above (Wood et al., 2005; Hassan et al., 2008), our genome-wide analysis of microsatellite data shows that populations generally cluster on the basis of both geographic region and linguistic classification. Fig. 5.3 demonstrates that populations generally separate by linguistic affiliation along dimension 1. Dimension 2 separates the SAK speakers from all other Africans including the eastern Khoesan speakers, the Hadza and Sandawe, that cluster closely with other eastern Africans. Another interesting pattern that emerges in the MDS plot that is consistent with previous work (Tishkoff et al., 2009) is the clustering of the Afroasiatic Chadic speakers with the Nilo-Saharan speakers, which may reflect a past language shift (Tishkoff et al., 2009).

Because the distribution of language families in Africa roughly follows a geographic distribution (Fig. 5.1), we also performed MDS within geographic regions that include at least three language families. In central Africa (Fig. 5.4), the samples cluster by language family with a few notable exceptions. For example, the Fulani who are nomadic pastoralists that speak a Niger-Kordofanian language and reside across central and western Africa do not cluster with other Niger-Kordofanian-speaking populations. Moreover, the Fulani are distinguished from other African samples at $K = 14$ in Tishkoff et al.'s (2009) STRUCTURE analysis. Morphological analyses of the Fulani have been interpreted to suggest a Middle Eastern

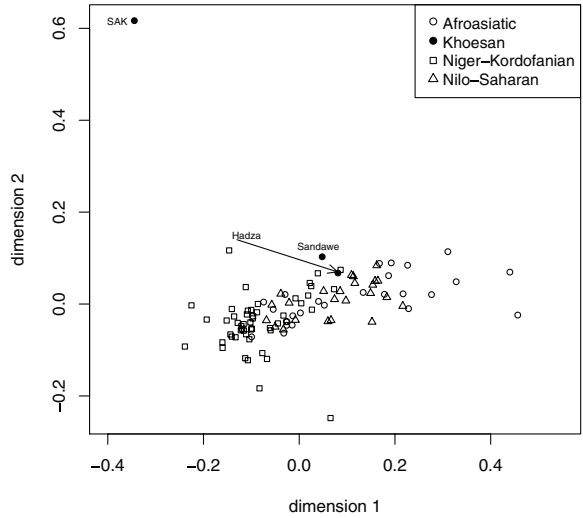


FIGURE 5.3 Multidimensional scaling (MDS) analysis of autosomal microsatellite data from Tishkoff et al. (2009). A pairwise genetic distance matrix using $(\delta\mu)^2$ [as described in Tishkoff et al. (2009)] was constructed for populations with a sample size of $n \geq 10$ and used for MDS analysis. Populations are distinguished on the basis of linguistic affiliation. The Afroasiatic speakers are displayed as open circles, the Nilo-Saharan speakers are displayed as triangles, the Khoesan speakers are displayed as filled circles, and the Niger-Kordofanian speakers are displayed as squares. The Khoesan speakers are labeled. The *x* axis represents dimension 1 and the *y* axis represents dimension 2.

origin for the Fulani (Ehret, 2008), and there has been some speculation based on linguistic data that the Fulani migrated to central Africa from northern Africa or the Middle East (Ehret, 2008). In addition, there is evidence of shared recent ancestry and/or gene among the Fulani and European/Middle Eastern samples from studies of mtDNA (Cerny et al., 2006), NRY (Hassan et al., 2008), and autosomal microsatellites (Tishkoff et al., 2009) and from the presence in this population of the mutation associated with lactose tolerance in Europeans (T-13910) (Mulcare et al., 2004).

Whereas previous work on mtDNA (Cerny et al., 2006) is consistent with a West African origin for the Fulani (consistent with their Niger-Kordofanian language classification), the NRY data reveal that the Fulani share recent ancestry with Nilo-Saharan- and Afroasiatic-speaking populations (Hassan et al., 2008). As in other cases where the maternal and paternal patterns of population history are not in agreement, this result could reflect differential patterns of Fulani male and female migration and gene flow, or it could reflect the influence of genetic drift or some

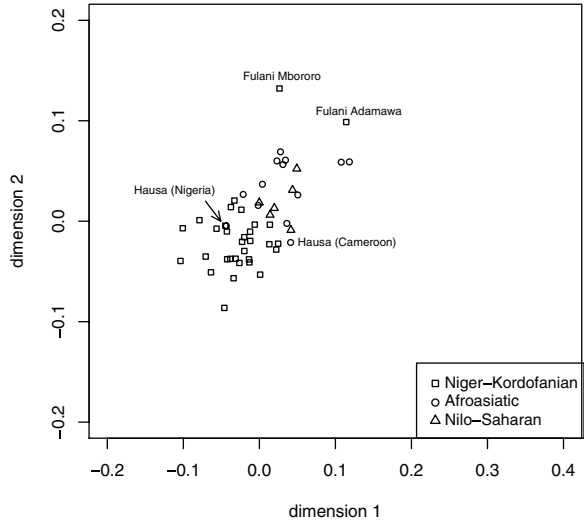


FIGURE 5.4 Multidimensional scaling (MDS) ($k = 2$) analysis of data from Tishkoff et al. (2009). We included central African populations with a sample of $n \geq 10$, constructed a pairwise distance matrix using $(\delta\mu)^2$ (as described in Tishkoff et al., 2009), and the population samples are displayed by linguistic affiliation. The Afroasiatic speakers are shown as open circles, the Nilo-Saharan speakers are shown as triangles, and the Niger-Kordofanian speakers are shown as squares. The Fulani and Hausa population samples are labeled. The $x$ axis represents dimension 1 and the $y$ axis represents dimension 2.

combination of the two. A more recent analysis of genome-wide autosomal data shows that the Fulani, who form a distinct population cluster, show genetic similarities with the Chadic- and Central Sudanic-speaking populations (Tishkoff et al., 2009). This result is consistent with our MDS analysis in which both Fulani cluster most closely with the Chadic- and Central Sudanic-speaking populations, as well as with the Baggara (Semitic). The clustering of the Baggara near the Fulani is also consistent with Tishkoff et al. (2009), who report that the Baggara share ancestry with the Fulani and with the Chadic speakers.

To a lesser extent, the Hausa from Nigeria and Cameroon cluster more closely with the Niger-Kordofanian speakers along dimension 2 (Fig. 5.4). This result is consistent with previous genetic analysis (Tishkoff et al., 2009) and with linguistic analysis of the Hausa that suggests extensive interaction between the Hausa (who speak an Afroasiatic Chadic language) and Niger-Kordofanian speakers as evidenced by an analysis of loanwords (Ehret, 2006).

In eastern Africa (Fig. 5.5, dimension 1 separates the Afroasiatic and Niger-Kordofanian samples, and dimension 2 separates the Nilo-Saharan samples. As in Fig. 5.3, the Hadza and Sandawe do not separate from the eastern African samples along either dimension to any large extent, although they do cluster closely to each other (Fig. 5.5), and this pattern is consistent with extensive regional gene flow with neighboring populations. The other noteworthy pattern in this plot is the Luo sample (Fig. 5.5), who speak a Western Nilotic language but cluster separately from other Nilo-Saharan speakers along dimension 1, together with Bantu-speaking populations. This clustering is consistent with previous findings that the Luo show predominately Bantu ancestry (Tishkoff et al., 2009) and may reflect high levels of admixture among the Luo and geographically nearby Bantu populations (Bennett, 1983).

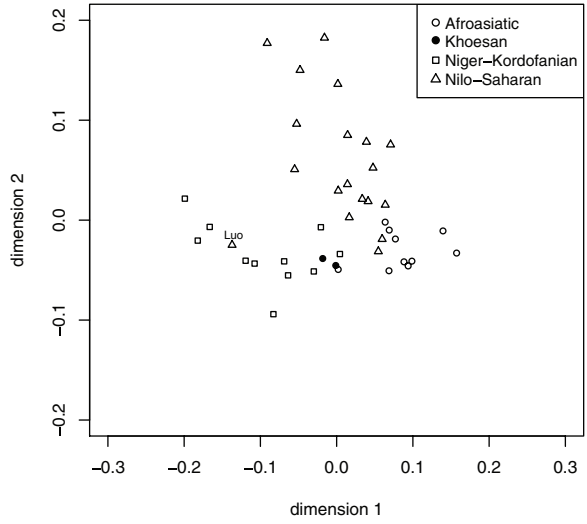


FIGURE 5.5 Multidimensional scaling (MDS) ($k$ = 2) analysis of data from Tishkoff et al. (2009). We included eastern African populations with a sample of $n \geq 10$, constructed a pairwise distance matrix using $(\delta\mu)^2$ (as described in Tishkoff et al., 2009), and the population samples are displayed by linguistic affiliation. The Afroasiatic speakers are shown as open circles, the Nilo-Saharan speakers are shown as triangles, the Khoesan speakers are shown as filled circles, and the Niger-Kordofanian speakers are shown as squares. The Luo population sample is labeled. The $x$ axis represents dimension 1 and the $y$ axis represents dimension 2.

**History of Hunter-Gatherer Populations**

As mentioned previously, the classification of languages within the Khoesan language family is contentious given the high diversity within each subclade and extreme divergence among them (Sands, 1998; Ehret, 2000), particularly for the Sandawe and Hadza. A common classification, therefore, groups the three languages spoken in South Africa into a separate branch (SAK) from the more divergent Sandawe and Hadza (Heine and Nurse, 2000). One interpretation of this extreme linguistic diversity is that the last common ancestor of the language family must be extremely ancient, and Ehret (2000) estimates the TMRCA to be at least 20 kya (which approaches the limit in timescale to linguistic reconstruction). The Sandawe and SAK are more similar to each other linguistically than either one is to the Hadza. Geographically, however, the Sandawe and Hadza are extremely close to each other (150 km apart in Tanzania), and both are geographically distant from the SAK populations residing in southern Africa.

A recent study of mtDNA and NRY variation investigates the genetic relationship among the Hadza, Sandawe, and SAK (Tishkoff et al., 2007a). The authors find that in general, the Hadza and Sandawe are more genetically similar to each other than either one is to the SAK. However, the Sandawe and SAK share ancient mtDNA lineages, which may suggest an ancient common ancestry. For example, mtDNA haplogroup L0d is present at high frequency in the SAK and at low frequency in the Sandawe, but is not present in the Hadza samples (Tishkoff et al., 2007a), and the TMRCA estimate of the SAK and Sandawe L0d lineages is ancient (~60 kya) (Tishkoff et al., 2007a). Similarly, the SAK and Sandawe share NRY haplogroup A (M91), which is not present in the Hadza samples (Tishkoff et al., 2007a). On the other hand, haplogroup L4g is common in both the Sandawe and the Hadza and absent from the SAK samples, and the TMRCA for the Sandawe and Hadza L4g is more recent (~25 kya) (Tishkoff et al., 2007a). And all three samples share NRY haplogroup B2b (M112) (Tishkoff et al., 2007a). The authors (Tishkoff et al., 2007a) discuss more than one interpretation of these results. The absence of mtDNA haplogroup L0d and NRY haplogroup A (M91) from the Hadza could reflect loss due to genetic drift because there is evidence of a recent bottleneck in the Hadza (Blurton Jones et al., 1992). Alternatively, the pattern of haplogroup variation could reflect an ancient linguistic and genetic divergence of the Hadza from the SAK. Moreover, the authors (Tishkoff et al., 2007a) performed a likelihood analysis to estimate the time of divergence among the populations and found that the divergence between the Hadza and the Sandawe was >20 kya and the divergence between the Hadza/Sandawe and the SAK was >40 kya. Additional studies of mtDNA and NRY variation have identified ancient shared lineages among the SAK and the Hadza as well as

several other eastern African populations (Underhill et al., 2000; Cruciani et al., 2002; Semino et al., 2002, 2004; Knight et al., 2003). Consistent with the mtDNA and NRY data, our MDS analysis shows that the Hadza and Sandawe cluster closely together with each other and with other eastern African populations (Fig. 5.3). Additionally, the Hadza are slightly farther from the SAK than the Sandawe along both dimensions (Fig. 5.3).

Tishkoff et al. (2009) provide evidence for an ancient common ancestry of Khoesan and Pygmy populations, suggesting the possibility of a proto-Khoesan hunter-gatherer population in eastern Africa that diverged >30 kya. STRUCTURE analysis revealed that the pygmies cluster together with other hunter-gatherer samples, including the SAK, Hadza, and Sandawe at low $K$ values ($K$ = 3), and then differentiate at higher $K$ values ($K$ = 5) (Table 5.1). The analysis also shows that the Mbuti pygmies cluster with the SAK at higher $K$ values ($K$ = 7), which could be due to either common ancestry or more recent gene flow. In addition, recent work on mtDNA, NRY, and autosomal data estimated the TMRCA of the pygmy and agricultural populations to be approximately 70–60 kya and the TMRCA of western and eastern pygmies to be approximately 20 kya (Destro-Bisol et al., 2004; Quintana-Murci et al., 2008; Patin et al., 2009). The findings of Tishkoff et al. (2009) raise the possibility that the pygmy populations, who have lost their indigenous language, once spoke some form of proto-Khoesan with click consonants. Interestingly, linguistic analysis of the SAK suggests that they originated in eastern Africa and possibly as far north as Ethiopia before migrating into southern Africa, consistent with the identification of rock art in the Sandawe homeland and in southern Africa that is thought to be related to Khoesan speakers (Lim, 1992). There is further evidence that, although there has not been recent gene flow among these populations, there has been recent admixture between the Sandawe and neighboring populations as well as between the pygmies and neighboring populations, and this recent admixture may be obscuring the more ancient relationships among the hunter-gatherer populations (Tishkoff et al., 2009). Future analyses that incorporate data from across the genome together with full-likelihood or approximate Bayesian computation methods will be necessary to more fully understand these complex population histories.

## CONCLUSIONS

We have presented here a synthesis of the archaeological, linguistic, and genetic data used to infer African population history. The general picture that emerges is that genetic variation in Africa is structured geographically and to a lesser extent linguistically. This is consistent with the fact that populations in close geographic proximity to each other as well

as populations that speak linguistically similar languages are more likely to exchange genes. The pattern of genetic variation in Africa is also consistent with geographic barriers limiting gene flow as exampled by the geographic/genetic distinction between northern African and sub-Saharan African populations. When we focus, however, on particular exceptions to these broad patterns, we are able to more fully appreciate the complex population histories that have contributed to extant patterns of genetic variation. The development of sequencing and genotyping technologies is advancing at an unprecedented rate and is allowing for the genotyping of millions of single-nucleotide polymorphisms and the sequencing of millions of nucleotides across populations. These data, coupled with computational methods for inferring demographic parameters and testing demographic models (e.g., maximum likelihood and approximate Bayesian computation), are well powered to refine our understanding of African past population histories. The incorporation of archaeological and linguistic data will be important for establishing testable hypotheses and elucidating the evolutionary processes (or forces) that have shaped the genomic landscape in Africa.

## ACKNOWLEDGMENTS

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# Part II

## STRUCTURE AND FUNCTION OF THE HUMAN GENOME

The first published reports of the complete nucleotide sequence of a human genome appeared near the turn of the 21st century (Lander et al., 2001; Venter et al., 2001), and the full sequence of a chimpanzee genome was unveiled soon thereafter (Chimpanzee Sequencing and Analysis Consortium, 2005). Overall, humans and chimpanzees proved to be about 99% identical in the nucleotide regions they share (which include most of the genome and essentially all genes). Thus, somewhere within that "other 1%" of the nucleotide sequence must reside all of the genetic changes that biologically differentiate humans from our closest living relatives. The "smallness" of the genetic divergence can be deceptive; a 1% sequence difference means that the human and chimpanzee genomes differ at about 30,000,000 among their 3 billion pairs of nucleotides. A monumental challenge for the field of evolutionary genetics is to pinpoint the specific genomic alterations that causally underlie (and precisely how so?) various unique features that make us human.

In Chapter 6, Ajit Varki describes an apparent "hotspot" in human genomic evolution, involving multiple loci that encode or regulate the expression of sialic acids (Sias) and the receptors that recognize them. The Sias are ubiquitous molecules that "decorate the canopy of the glycan forest" on cell surfaces and thereby play several key roles in human health and disease, for example by serving as cell-surface signals for "self" recognition in the vertebrate immune system, or as cell-surface targets for the extrinsic receptors of many pathogens. By comparing the suite of human sialic acids and their associated binding proteins against those of

nonhuman primates, Varki details the molecular bases and the putative functional consequences of more than 10 evolutionary genetic changes that seem to be specific to the human lineage. Overall, Varki's analyses reveal multifaceted and oft-unexpected roles for cell-surface molecules in human biology and evolution. The sialic acid story also has broader evolutionary ramifications. For example, it implies that evolutionary "arms races" between hosts and pathogens can promote a form of "molecular mimicry" whereby different microorganisms convergently "reinvent" the use of Sias to help mask themselves from the surveillance of vertebrate immune systems. The Sias system also illustrates the profound challenges as well as the opportunities that likely will attend many such attempts to dissect other complex structural and functional components of human genome evolution.

Conventionally, "the human genome" refers to the full suite of DNA within the cellular nucleus. However, the nuclear genome has a diminutive partner—mitochondrial (mt) DNA—housed in the cellular cytoplasm. The prototypical human mitochondrial genome is only 16,569 base pairs in length (roughly a half-million-fold smaller than each nuclear genome), but what mtDNA lacks in size it more than makes up for in terms of copy number (thousands of mtDNA molecules reside in a typical somatic cell) and functional significance. Proteins and RNAs coded by the mitochondrial genome contribute critically to mitochondrial operations, which provide the cell with its chemical energy. The first complete sequence of human mtDNA was published 30 years ago (Anderson et al., 1981) and since then this "other" genome has become a model system for genealogical reconstructions of human demographic history (Cann et al., 1987) as well as for mechanistic appraisals of genomic structure and function in relation to human health (Wallace, 2005; McFarland et al., 2007). These topics have been thoroughly reviewed elsewhere, but in Chapter 7, Douglas Wallace uses such informational backdrop as a springboard to launch a bioenergetic hypothesis that ascribes a central role for energy flux in generating and maintaining complex biological structures such as the human brain. Wallace envisions a cyclical evolutionary process in which complex adaptations arise from a synergy between the information-generating power of energy flow and the information-accumulating capacity of selection-winnowed DNA. Under this evolutionary scenario, bioenergetic genes (notably those contributing to mitochondrial function) play key roles.

The ongoing genomics revolution in biology that began little more than decade ago is opening new windows not only to the genes that make us human but also to the nature and significance of genetic differences between extant human populations now living in different geographical regions of the planet. As a part of this global monitoring effort by the scientific community (Rosenberg et al., 2002; Frazer et al., 2007), Katarzyna

Bryc and others associated with the laboratory of Carlos Bustamante provide, in Chapter 8, a detailed case study involving mostly Hispanic/Latino populations in Central and South America. The authors compile and analyze genotypic information for several thousand individuals at several tens of thousands of SNPs (single-nucleotide polymorphisms) scattered across the two human genomes (nuclear and mitochondrial). The results reveal a complex genetic signature of recent sex-biased admixture superimposed on a potentially ancient substructure involving source populations of Native American, European, and West African ancestry. In addition to illuminating the genealogical heritage of particular human populations, genomic surveys of this sort, when interpreted in combination with detailed epidemiological data, should also be helpful in studies of the spatial distributions and evolutionary-genetic etiologies of particular human heritable diseases.

In Chapter 9, Nina Jablonski and George Chaplin show how, even in the age of genomics, much can still be learned about adaptive human evolution from comprehensive geographical analyses of phenotypes, in this case involving the most obvious of all human polymorphisms: skin pigmentation. Although the precise mechanistic action of the full suite of pigmentation genes underlying human skin-color variation remains incompletely known, the authors erect a compelling adaptationist scenario for why humans generally evolved dark skins near the equator and depigmented but tannable skins at intermediate and higher latitudes. This striking latitudinal pattern appears to reflect selection-mediated responses to two distinct challenges related to exposure to ultraviolet radiation (UVR), major forms of which (UVA and UVB) vary predictably with latitude and season. In the tropics, where UVA is high year-round, dark pigmentation tends to be selectively advantageous because it protects the body against damaging UVR exposure. At higher latitudes, where UVB levels generally are lower and peak only once per year, natural selection has tended to favor light but tannable skin that can capture UVB for the cutaneous production of vitamin D, which otherwise must come from a suitable diet. As detailed by Jablonski and Chaplin in their opening comments, this modern understanding of skin color variation in humans is strikingly different not only from some of the racially prejudiced ideas formerly in vogue, but also from the sexual-selection hypothesis for skin pigmentation favored by Darwin in *The Descent of Man*.

Before Darwin, most scientists as well as theologians accepted what seemed obvious: that divine intervention must have underlain nature's design. The traditional "argument from design" traces back at least to the classical Greek philosopher Socrates more than 400 BC [see Sedley (2008)], and it was expressed again in a thoughtful treatise entitled *Natural Theology* by the Reverend William Paley (1802). Darwin later recalled in his

autobiography [see Barlow (1958)] that Paley's logic "gave me as much delight as did Euclid" and that it was the "part of the Academical Course [at the University of Cambridge] which . . . was the most use to me in the education of my mind." Darwin himself was a natural theologian when he boarded the *Beagle* in 1831 on what would be a fateful voyage into previously uncharted scientific waters. Darwin's discoveries were revolutionary for philosophy and theology as well as science because they identified a nonsentient directive agent (natural selection) that apparently could craft complex and beautiful biological outcomes that otherwise would be interpreted as direct handiworks of God. In Chapter 10, John Avise asks whether the human genome displays the kinds of artistry of molecular design that natural theologians might wish to claim as definitive proof for *ex nihilo* craftsmanship by a caring and omnipotent Deity (Behe, 1996). To the contrary, modern genetic and biochemical analyses have revealed, unequivocally, that the human genome is replete with mistakes, waste, dead-ends, and other molecular flaws ranging from the subtle to the egregious with respect to their negative impacts on human health (Avise, 2010). These are the kinds of biological outcomes that are expected from nonsentient evolutionary processes, but surely not from an intelligent designer. Avise argues, nevertheless, that theologians should welcome rather than disavow these genomic discoveries. The evolutionary sciences can help to emancipate mainstream religions from the age-old theodicy dilemma (the theological "problem of evil") and thereby return religious inquiry to its rightful realm—not as the secular interpreter of biological minutiae of our physical existence, but rather as a respectable counselor on grander philosophical matters that have always been of "ultimate concern" (Dobzhansky, 1967) to theologians, and to humanity.

# 6

# Uniquely Human Evolution of Sialic Acid Genetics and Biology

AJIT VARKI

Darwinian evolution of humans from our common ancestors with non-human primates involved many gene–environment interactions at the population level, and the resulting human-specific genetic changes must contribute to the "Human Condition." Recent data indicate that the biology of sialic acids (which directly involves less than 60 genes) shows more than 10 uniquely human genetic changes in comparison with our closest evolutionary relatives. Known outcomes are tissue-specific changes in abundant cell-surface glycans, changes in specificity and/or expression of multiple proteins that recognize these glycans, and novel pathogen regimes. Specific events include Alu-mediated inactivation of the *CMAH* gene, resulting in loss of synthesis of the Sia *N*-glycolylneuraminic acid (Neu5Gc) and increase in expression of the precursor *N*-acetylneuraminic acid (Neu5Ac); increased expression of α2–6-linked Sias (likely because of changed expression of *ST6GALI*); and multiple changes in *SIGLEC* genes encoding Sia-recognizing Ig-like lectins (Siglecs). The last includes binding specificity changes (in Siglecs -5, -7, -9, -11, and -12); expression pattern changes (in Siglecs -1, -5, -6, and -11); gene conversion (*SIGLEC11*); and deletion or pseudogenization (*SIGLEC13*, *SIGLEC14*, and *SIGLEC16*). A nongenetic outcome of the *CMAH* mutation is human metabolic incorporation of foreign dietary Neu5Gc, in the face of circulat-

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ing anti-Neu5Gc antibodies, generating a novel "xeno-autoantigen" situation. Taken together, these data suggest that both the genes associated with Sia biology and the related impacts of the environment comprise a relative "hot spot" of genetic and physiological changes in human evolution, with implications for uniquely human features both in health and disease.

The theory of evolution via descent by natural selection explains the diversity of life on Earth (Darwin, 1859). Huxley (1863) and Darwin (1871b) correctly predicted that the "great apes" (chimpanzees, bonobos, gorillas, and orangutans, i.e., nonhuman hominids, NHHs[1]) are our closest evolutionary cousins. Indeed, chimpanzees were once considered good models for human disease. However, there are major differences between humans and NHHs in the incidence and severity of various diseases, beyond those explained by anatomical reasons (Varki, 2000; Varki and Altheide, 2005; Finch, 2010).

Scholars of mathematical, physical, and chemical sciences sometimes ask why biology does not have the kinds of universal laws that underpin their disciplines. The reason is that although biological systems operate under mathematical, physical, and chemical principles, evolutionary mechanisms of random mutation and deterministic selection do not generate consistent or universal outcomes. Of course, a single origin of life combined with physical constraints resulted in some near-universals, such as the paradigm that nucleic acid sequences encode protein sequences (Crick, 1970). Another apparent biological universal is that all nucleated cells in nature are covered with a dense and complex coating of sugar chains (glycans) (Varki, 2006), which have numerous biological roles (Varki and Lowe, 2009). Thus, natural selection repeatedly recruited glycans as being the best molecules for decorating the cell surface. Here I focus on one aspect of cellular glycan coating that changed during human evolution, potentially explaining aspects of human uniqueness, in health and in disease.

[1]The term "great ape" refers to chimpanzees, bonobos, gorillas, and orangutans, and the term "hominoid" also includes lesser apes. Neither term is now taxonomically valid. The term "hominid" is now being used for the clade including humans and great apes. I here mostly use the term "nonhuman hominid" (NHH) in place of great ape and the term "hominin" for branches of the human-like lineages after the common ancestor with chimpanzees.

## SIALIC ACIDS DECORATE THE CANOPY OF THE CELL-SURFACE GLYCAN FOREST AND HAVE MULTIPLE BIOLOGICAL ROLES

In the *Deuterostome* lineage (vertebrates and so-called "higher" invertebrates) the outer ends of glycan chains are often capped by sialic acids (Sias) (Varki, 2007; Schauer, 2009). Biosynthetic pathways for these nine-carbon backbone molecules likely evolved from those for ancestral non-ulosonic acids (Lewis et al., 2009). Although Sias are rare in other taxa (with the exception of certain pathogenic/commensal bacteria, as discussed later) they are ubiquitous on all vertebrate cell surfaces and are essential for embryonic development (Schwarzkopf et al., 2002). Indeed, they mediate many critical endogenous functions by virtue of physical properties and via recognition by intrinsic receptors (Varki, 2007; Schauer, 2009). Also, cell-surface Sias are used by complement factor H (Pangburn et al., 2000) and by Sia-binding Ig-like lectins (Siglecs) (Varki and Angata, 2006; Crocker et al., 2007) as signals for "self" recognition in the vertebrate innate immune system. However, given their location and abundance (dozens to hundreds of millions of copies on each cell), Sias also are targets for extrinsic receptors of numerous pathogens (Varki, 2007). Meanwhile, Sias have been "reinvented" repeatedly via convergent evolution by microbes that interact with vertebrates (Vimr et al., 2004; Lewis et al., 2009). Such "molecular mimicry" allows microorganisms to use Sias not only to mask themselves from the complement and adaptive immune systems (Pangburn et al., 2000; Schauer, 2009) but also to engage the Siglecs (as discussed later), dampening the innate immune response (Carlin et al., 2009b). For all these reasons, Sias are at the nexus of an evolutionary arms race between vertebrate hosts and their pathogens, interactions characterized by many "Red Queen" processes (Varki, 2006; Varki and Angata, 2006). This competition may also explain why there are so many kinds of Sias, each presented in several different linkages to the underlying monosaccharide, on a variety of different types of glycans (Varki, 2007; Schauer, 2009).

## "SERUM SICKNESS" AS A CLUE TO HUMAN UNIQUENESS

Given the considerations discussed in the previous section, it is not surprising that differences in Sia expression are common between different taxa, even closely related ones. However, on closer inspection, such differences tend to be relative rather than absolute (Zanetta et al., 2001). One classic exception was a difficulty in finding the Sia *N*-glycolylneuraminic acid (Neu5Gc) in human tissues (Gottschalk, 1960). Indeed, humans make antibody responses against Neu5Gc during "serum sickness reactions" induced by animal serum infusion, characterized by antibodies agglutinating animal red blood cells bearing Neu5Gc (Higashi et al., 1977; Merrick et

al., 1978; Malykh et al., 2001). However, Neu5Gc was detected in human cancers and fetal tissues (Malykh et al., 2001).

## A SIA DIFFERENCE BETWEEN HUMANS AND NHHS

Besides Neu5Gc, the other major Sia on most mammalian cell types is *N*-acetylneuraminic acid (Neu5Ac). These molecules differ by one oxygen atom, which is added to CMP-Neu5Ac in the cytosol, in a reaction catalyzed by the enzyme cytidine monophosphate *N*-acetylneuraminic acid hydroxylase (CMAH) (Shaw and Schauer, 1989; Takematsu et al., 1994). Both CMP-Neu5Ac and CMP-Neu5Gc are transported into the Golgi, where they are donors for addition of these Sias to many glycoconjugates. Thus, most mammalian tissues contain both Sias. In contrast, Neu5Gc was claimed to be missing in normal human tissues (Gottschalk, 1960). We showed that whereas all NHHs had easily detectable Neu5Gc in erythrocytes and plasma proteins, it was indeed missing from normal human blood samples (Muchmore et al., 1998). This human-specific difference was explained by deletion of a critical 92-base-pair exon in the *CMAH* gene (Chou et al., 1998; Irie et al., 1998)[2] encoding key amino acids required for enzymatic function. This single *Alu*-mediated mutation (Hayakawa et al., 2001) occurred in one ancestral hominin *CMAH* gene, an allele now universal to humans. Timing was estimated to be ~2–3 Mya (Chou et al., 2002), which is, interestingly, just before emergence of the genus *Homo* (Wood and Collard, 1999). Of course, any genomic signatures of selection are erased by such depths of evolutionary time.

## HUMAN-SPECIFIC Neu5Gc LOSS AFFECTS PATHOGEN REGIMES

The loss of Neu5Gc and resulting excess of Neu5Ac (Fig. 6.1, step 1) would have affected relative efficacy of interactions of various pathogens with humans. Humans should be resistant to pathogens binding Neu5Gc (Kyogashima et al., 1989; Rolsma et al., 1998; Martin et al., 2005; Schwegmann-Wessels and Herrler, 2006; Campanero-Rhodes et al., 2007) and more susceptible to pathogens preferring to bind Neu5Ac. Particularly interesting is a difference in erythrocyte Sia-binding preference between malarial parasites of humans and African NHHs (Martin et al., 2005).

[2]There is a discrepancy between the two original reports, one of which claimed *N*-terminal protein truncation (Irie et al., 1998), and the other, which concluded that the *N* terminus is intact, and a frame shift resulted (Chou et al., 1998) from the 92-base-pair exon deletion. The second scenario appears more likely correct, as the first assumed an "in frame" start codon.

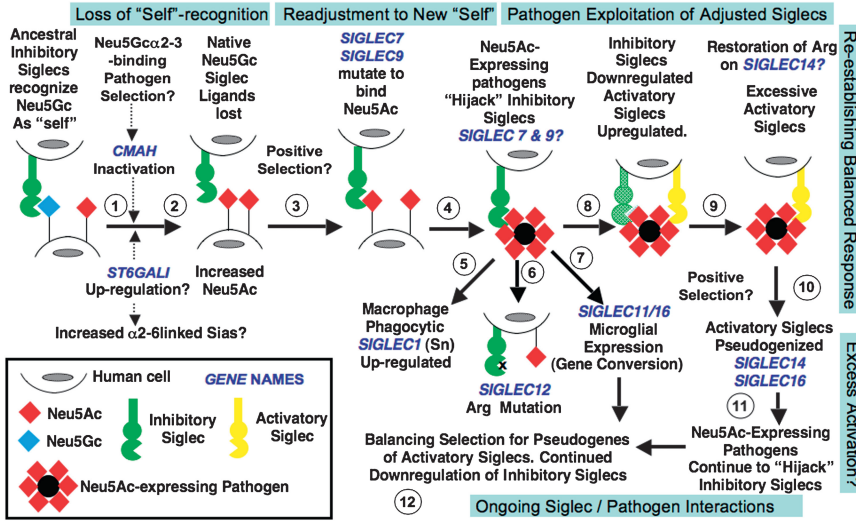
Indeed, we and others suggested that ancestral hominins escaped the prevailing NHH malaria by eliminating Neu5Gc production and that *Plasmodium falciparum* (today's human "malignant malaria") arose later, when a strain of the NHH malaria evolved to be able to bind preferentially to Neu5Ac-rich erythrocytes of humans (Rich et al., 2009; Varki and Gagneux, 2009). Further studies of Neu5Gc and Neu5Ac preferences of human and nonhuman pathogens are warranted.

## DIFFERENTIAL EXPRESSION OF α2–6-LINKED SIAS BETWEEN HUMANS AND NHHS

Influenza viruses use Sias as binding targets, and strains infecting some other species do not easily "jump" into humans. However, this difference is not primarily explained by human Neu5Gc deficiency, because these viruses show only relative preferences for the two Sias (Suzuki et al., 2000). A bigger difference lies in the finding that although avian influenza viruses preferentially recognize Sias α2–3-linked to the underlying sugar chain, human viruses prefer the α2–6-linked variety (Daniels et al., 1984). This difference corroborates with α2–6-linked Sia expression on human upper airways (Baum and Paulson, 1990). Meanwhile, chimpanzees challenged with human influenza virus did not show severe infections (Snyder et al., 1986). In keeping with this finding, we found low expression of α2–6-linked Sias in upper airways of NHHs (i.e., more similar to their expression in mice and birds) (Gagneux et al., 2003). This difference likely results from preferential human up-regulation of the enzyme ST6Gal-I, which determines expression of α2–6-linked Sias (Appenheimer et al., 2003) in humans. One possibility is that malarial parasites that preferentially bind α2–3-linked Sias (Orlandi et al., 1992) could have selected for up-regulation of α2–6-linked Sias on ancestral hominin erythrocytes (Gagneux et al., 2003) and thus, secondarily, in other tissues (Fig. 6.1, step 1).

## SIGLECS DIFFERENCES BETWEEN HUMANS AND NONHUMAN HOMINIDS

Siglecs are a family of Sia-binding proteins characterized by amino-terminal V-set Ig-like domains with a Sia-binding site (Varki and Angata, 2006; Crocker et al., 2007) followed by variable numbers of C2-set domains, a single transmembrane domain, and varying lengths of cytosolic tails that may or may not have signaling domains—typically immunoreceptor tyrosine-based inhibitory motifs (ITIMs), which can recruit the tyrosine phosphatases SHP-1 or SHP-2 and down-regulate cellular activation by antagonizing tyrosine kinase action (Varki and Angata, 2006; Crocker et al., 2007). Siglec homologs are present in most vertebrates (Cao et al.,




See Figure 6.1 caption on facing page.

2009) and seem prominent in primates (Angata et al., 2004). One subclass called "CD33-related Siglecs" (CD33rSiglecs) is rapidly evolving via multiple genomic processes (Angata et al., 2004). Multispecies genomic BAC sequencing of the CD33-related Siglec gene cluster (Angata et al., 2004) followed by chimpanzee genome sequencing made it possible to clone and characterize what may be all 16 hominid Siglecs. Remarkably, as discussed later, human-specific differences from other NHHs have been found in many CD33rSiglecs.

## HUMAN-SPECIFIC ADJUSTMENTS IN SIA RECOGNITION BY SIGLECS

The ancestral condition of hominid Siglecs appears to have been to recognize Neu5Gc preferentially (Sonnenburg et al., 2004). This supposition fits with the function of CD33rSiglecs to recognize Sias as "self" and send dampening signals to immune cells via cytosolic tail ITIMs (Varki and Angata, 2006; Crocker et al., 2007; Carlin et al., 2009b). Because no pathogen has been reported to synthesize Neu5Gc, and many can synthesize Neu5Ac, Neu5Gc should indeed be the preferred molecule for "self" recognition. Thus, when human ancestral hominins lost Neu5Gc, many CD33rSiglecs would have lost their preferred ligand (Fig. 6.1, step 2), likely causing excessive innate immune cell activation. Although this loss may even have been beneficial in short-term defense, it would be eventually

FIGURE 6.1 Proposed evolutionary scenario linking human-specific changes in Sia-related genes. It is impossible to conclusively prove evolutionary events and selection factors affecting Sia biology before the origin of modern humans. The speculative scenario presented here is based on available information and takes the parsimonious view that the events are related to one another. The first event may have been loss of Neu5Gc expression via *CMAH* inactivation and fixation (steps 1 and 2). A possible selection mechanism was a Neu5Gc-binding pathogen such as an NHH malaria, combined with genetic drift caused by ancestral demography. Because such organisms prefer binding α2–3-linked Sias, the increased human expression of α2–6-linked Sias may have been related. Human pathogen regimes would also have changed because of loss of Neu5Gc and excess of Neu5Ac. Some outcomes may have been positive (i.e., temporary escape from preexisting pathogens), and others may have been negative (e.g., increased susceptibility to Neu5Ac-binding pathogens and inability to modulate Neu5Gc/Neu5Ac ratios). Meanwhile, the loss of Neu5Gc should have resulted in loss of CD33rSiglec ligands needed for "self-recognition" (step 3). The likely hyperimmune state following Siglec ligand loss would have been followed by positive selection to allow multiple Siglecs (e.g., Siglec-9 and -7) to recognize Neu5Ac (step 4). Following this readjustment to the new "self," a new risk would emerge. Although microbes appear incapable of synthesizing Neu5Gc, they have repeatedly reinvented Neu5Ac in multiple ways. Such pathogens would now be able to "hijack" inhibitory Siglecs such as Siglec-7 and -9, dampening the innate immune response of hominins (step 4). Indeed, several such organisms tend to be human-specific commensals. Notably, this proposed phase of pathogen exploitation of adjusted Siglecs is also the period of human evolution when newborns were becoming increasingly immature and more susceptible to these types of pathogens, especially those involved in brain invasion. Macrophage Siglec-1 might have then been up-regulated to enhance phagocytosis of Neu5Ac-expressing pathogens (step 5). Consequences of this proposed episode of pathogen exploitation of adjusted Siglecs could have been mutations of the Arg residue required for Sia recognition (Siglec-12, step 6) and the gene conversion event in Siglec-11 associated with recruitment to brain microglia (step 7). Eventually, immune cells would have down-regulated inhibitory Siglecs to escape the Neu5Ac-expressing pathogens while also up-regulating activatory Siglecs to respond to them (step 8). Perhaps this process explains why the critical Arg residue of the activatory Siglec-14 may have been restored in humans. This attempted reestablishment of a balanced response may have resulted in excessive activatory Siglecs (step 9), perhaps explaining the tendency of activatory Siglecs to be pseudogenized in modern humans (step 10). Of course, pathogens always evolve faster, and Neu5Ac-expressing pathogens are likely continuing to evolve to "hijack" our inhibitory Siglecs (step 11). Thus we likely have ongoing adjustments, with balancing selection for pseudogenes of the remaining activatory Siglecs and continued down-regulation of inhibitory Siglecs (step 12). It is also possible that these complex episodes of selection resulted in a changed profile of Siglec expression and function, not only in the innate immune system but also in other organs such as the placenta and the brain. Note that the human-specific changes in *SIGLEC6* (placental trophoblast expression) and *SIGLEC13* (deletion) are not incorporated into this model.

detrimental for reproductive fitness because of disease processes related to excessive immune responses. In keeping with this reasoning, human Siglecs studied show a preference for Neu5Ac over Neu5Gc (Sonnenburg et al., 2004). For this adjustment to occur, the V-set domain Sia-binding pockets of the CD33rSiglecs in ancestral hominins would have to be selected for multiple amino acid changes, switching either to specifically binding Neu5Ac or simply to accommodating it (Fig. 6.1, step 3). Indeed, sequence analyses indicate that this domain of CD33rSiglecs has undergone very rapid evolution in humans, even in comparison with relatively high rates in other taxa (Altheide et al., 2006). Taken together, the data suggest (Fig. 6.1) that lethality caused by Neu5Gc-binding pathogen (perhaps α2–3-linked Sia preferring) first selected the *CMAH*-null mutation, eliminating host Neu5Gc production. The resulting loss of "self" ligands for the CD33rSiglecs would have likely caused a hyperimmune state, perhaps with a temporary advantage. The next stage would have involved selection for amino acid changes to allow binding of Neu5Ac, restoring CD33rSiglec inhibitory function (Fig. 6.1, step 3).

## MANY HUMAN PATHOGENS EXPRESS Neu5Ac, POTENTIALLY ENGAGING CD33rSIGLECS AND ATTENUATING INNATE IMMUNE RESPONSES

The switch of human Siglecs toward binding Neu5Ac (presumably selected to restore proper "self" recognition) would have exposed humans to pathogens that could "reinvent" Neu5Ac via convergent evolution, thus "hijacking" inhibitory Siglec function to dampen innate immune responses (Fig. 6.1, step 4, and later discussion). Indeed, many microorganisms that express Neu5Ac appear to be human-specific commensals, becoming pathogenic when circumstances allow (Vimr et al., 2004). For example, Group B *Streptococcus* expresses a Sia-containing capsule that engages human neutrophil Siglec-9, dampening responses (Carlin et al., 2009b). Other sialylated pathogens are recognized by Siglecs (Jones et al., 2003), likely with similar outcomes (Khatua et al., 2009). Notably, such pathogens would have been a strong selective force, because they often affect fetuses, infants, and young adults and frequently cause lethal brain infections (Vimr et al., 2004).

## HUMAN-SPECIFIC CHANGES IN SIALOADHESIN ON MACROPHAGES

Sialoadhesin (Sialec-1, Sn) is a Siglec with 17 extracellular Ig-like domains, all conserved from mouse to human (Crocker et al., 1997). Also

conserved is the amino terminal V-set domain, which (even in the mouse) does not recognize Neu5Gc but binds only Neu5Ac, and only in α2–3 and α2–8 linkages (Crocker et al., 1997). Notably, Neu5Ac in α2–3 and α2–8 linkages are also the structures typically found on pathogens (Vimr et al., 2004). Furthermore, Sn is found primarily on macrophages, does not have a cytosolic signaling motif, and phagocytoses sialylated bacteria (Jones et al., 2003). Thus, although Sn has a role in modulating adaptive immunity (Oetke et al., 2006), a likely conserved function is to eliminate sialylated pathogens. Indeed, Sn in rodents is found at sites such as the sinuses of lymph nodes, spleen, and bone marrow that would first encounter bacteria invading extracellular fluids (Crocker et al., 1997) which filter blood or lymph-borne pathogens. In keeping with the human propensity for invasion by Neu5Ac-expressing pathogens, Sn is up-regulated in the human spleen compared with the chimpanzee (Brinkman-Van der Linden et al., 2000). In the chimpanzee, as in the rodent, only a subset of splenic macrophages is Sn positive, whereas in humans the distribution is more widespread (Brinkman-Van der Linden et al., 2000). Although more work is needed, current data suggest that Sn expression was up-regulated in humans, perhaps to deal with sialylated pathogens taking advantage of the Neu5Ac-preferring human CD33rSiglecs (Fig. 6.1, step 5). Interestingly, Sn is also up-regulated following inflammatory responses and in autoimmune diseases (Biesen et al., 2008) and has an additional role as a capture mechanism for certain viruses that have heavily sialylated envelope glycoproteins (Junt et al., 2007). In keeping with this notion, Sn-positive circulating monocytes may facilitate HIV entry into macrophages (Rempel et al., 2008), a viral invasion process prominent in humans.

## HUMAN-SPECIFIC CHANGES IN A CONSERVED ARGININE RESIDUE REQUIRED FOR SIGLEC RECOGNITION OF SIAS

All Siglecs studied to date have a conserved arginine (Arg) residue in the V-set domain, essential for Sia binding (Varki and Angata, 2006; Crocker et al., 2007). This Arg residue underwent a human-specific mutation in Siglec-12, a CD33rSiglec found on macrophages and epithelial surfaces (Angata et al., 2001). Interestingly, restoration of the Arg residue regenerates binding with a preference for Neu5Gc (Angata et al., 2001), suggesting that this Siglec may have been "retired" following human loss of Neu5Gc (Fig. 6.1, step 6). In the second instance, as discussed later, the Arg residue of Siglec-5 and Siglec-14 appears to be mutated in all NHHs, but restored in humans (Angata et al., 2006).

## HUMAN-SPECIFIC GENE CONVERSION INVOLVING SIGLEC-11

The gene encoding Siglec-11 is ~1 megabase away from the CD33rSiglec gene cluster on chromosome 19 (Angata et al., 2002) but has features of a CD33rSiglec, with a Sia-binding amino-terminal V-set domain and ITIMs in the cytosolic tail (Angata et al., 2002). The 5′ sequences of the *SIGLEC11* encoding the first two Ig-like domains showed a >99% similarity to the corresponding 5′ end of a nearby Siglec pseudogene *SIGLECP16* (Hayakawa et al., 2005). There is far less similarity in the rest of the sequences. Based on these and other data, we concluded that the *SIGLEC11* gene underwent a gene conversion by the 5′ sequences of *SIGLECP16,* generating a protein with a human-specific amino acid sequence (Hayakawa et al., 2005). Indeed, this gene conversion is not seen in the NHH Siglec-11 orthologs (Hayakawa et al., 2005). Moreover, it is human universal, indicating possible selection following gene conversion (Fig. 6.1, step 7). One consequence is a change in binding specificity toward a preference for Neu5Ac over the ancestral preference for Neu5Gc. Another consequence is that, although Siglec-11 is expressed in both human and chimpanzee tissue macrophages, it is selectively expressed in brain microglia only in humans (Hayakawa et al., 2005). This unusual brain expression could be related to the propensity of sialylated pathogens to invade the human brain and/or the fact that microglia have multiple roles in the brain beyond innate immunity (Lu et al., 2005).

In some humans the pseudogene *SIGLEC16P* locus can instead encode the functional gene sequence *SIGLEC16* (Cao et al., 2008), a molecule with potential activatory properties (as discussed later). Thus, some humans may have an activatory Siglec in brain microglia, and others may not. The population distribution of this segregating pseudo(gene) deserves further study. Consequences for microglia in human brain function and/or disease also need study.

## HUMAN-SPECIFIC EXPRESSION OF SIGLEC-6 IN THE PLACENTAL TROPHOBLAST WITH UP-REGULATION IN PREECLAMPSIA

Siglec-6 is an inhibitory CD33rSiglec expressed on B cells of both humans and NHHs (Brinkman-Van der Linden et al., 2007). However, it also shows human-specific placental expression, not in immune cells but in the trophoblast (Brinkman-Van der Linden et al., 2007). Placental expression is maximal following human labor and delivery (Brinkman-Van der Linden et al., 2007), suggesting a possible role in modulating the

unusual tempo of human labor, which lasts much longer in humans than in the NHHs (Brinkman-Van der Linden et al., 2007).

Preeclampsia is a human-specific pregnancy complication of unknown cause, characterized by hypertension, proteinuria, and vascular abnormalities in the placenta leading to fetal dysfunction and early labor (Winn et al., 2009). In a microarray comparison of placental mRNAs, one of the genes showing the highest expression increase in preeclampsia was *SIGLEC6* (Winn et al., 2009). It is interesting that both placental expression of Siglec-6 and preeclampsia itself are uniquely human phenomena. Many functional studies are needed, including analyses of placental Siglec-6 ligands (Brinkman-Van der Linden et al., 2007).

## CD33rSIGLECS ARE EXPRESSED AT LOW LEVELS ON HUMAN T CELLS ASSOCIATED WITH OVERREACTIVE RESPONSES TO ACTIVATION

Although CD33rSiglecs are found on most human immune cells, essentially no expression was found on $CD4^+$ T cells, and only low expression of Siglec-7 and -9 was found on $CD8^+$ T cells (Ikehara et al., 2004; Varki and Angata, 2006; Crocker et al., 2007). In contrast, there was easily detectable expression of multiple CD33rSiglecs (particularly Siglec-5) on all NHH T cells examined (Nguyen et al., 2006). Thus, suppression of inhibitory CD33rSiglec expression is a human-specific condition, perhaps related to the need to escape Neu5Ac-expressing pathogens (Fig. 6.1, step 8). Regardless of the reason, we found that human T cells reacted more strongly to stimulation (Nguyen et al., 2006; Soto et al., 2010). Down-regulation of Siglec-5 on the chimpanzee T cells allowed more proliferation, and forced expression in human T cells dampened responses (Nguyen et al., 2006). Thus, the human T cell is in a relatively overreactive state, a least partly because of lack of Siglec-5 expression. In this regard, humans seem more prone to diseases involving T-cell activation, including AIDS (Rutjens et al., 2003), chronic hepatitis (Bettauer, 2010), rheumatoid arthritis, and bronchial asthma (Varki, 2000). This relative overreactivity may also explain T-cell activation and excessive release of cytokines (a "cytokine storm") reported in human volunteers given a superactive anti-CD28 antibody (Stebbings et al., 2009) and the excessive human immune reactions in viral vector-based gene therapy trials (Mingozzi and High, 2007). More recently, we have found that human B cells are also relatively overreactive, compared with chimpanzee cells (Soto et al., 2010). Further studies are obviously needed, including any roles of activatory Siglecs (as discussed later).

## HUMAN-SPECIFIC PSEUDOGENIZATION OF ACTIVATORY SIGLECS

Some primate Siglecs have a charged residue in the transmembrane domain and lack a major cytosolic tail. In at least two known instances (Siglec-14 and -16) (Angata et al., 2006; Cao et al., 2008) these molecules associate with the adaptor DAP-12, recruiting its immunoreceptor tyrosine-based activatory motifs (ITAMs) and effectively converting them into activatory Siglecs. Interestingly, Siglec-14 is undergoing repeated 5'-end gene conversions with Siglec-5, so that its Sia-binding specificity remains the same (Angata et al., 2006). This feature is also true of Siglec-16, because of gene conversion with Siglec-11 (Hayakawa et al., 2005). Analogous to "paired" inhibitory and activatory killer Ig-like receptors (KIR) (Parham, 2005), the most likely explanation is that activatory Siglecs were originally selected to respond against Sia-expressing pathogens that were using inhibitory Siglecs to suppress immune responses (Fig. 6.1, steps 8 and 9). Interestingly, both Siglec-14 and Siglec-16 are pseudogenized in some humans (Cao et al., 2008; Yamanaka et al., 2009). Additionally, Siglec-13 has potential for being an activatory Siglec and has been deleted in the human genome (Angata et al., 2004). Overall, there were apparently multiple human-unique pseudogenization events involving activatory Siglecs. Perhaps an evolutionary episode of excessive CD33Siglec-mediated activation resulted in the need to reestablish a balanced response (Fig. 6.1, step 10). Of course, pathogens are always ahead in an evolutionary arms race, and humans may still be in a period of ongoing adjustments, involving continued "hijacking" of inhibitory Siglecs (Fig. 6.1, step 11) and balancing selection for pseudogenization of activatory Siglecs (Fig. 6.1, step 12).

## WAS SIA-RELATED BIOLOGY A "HOTSPOT" OF GENETIC AND PHYSIOLOGICAL CHANGES IN HUMAN EVOLUTION?

The high frequency of human-specific genetic changes associated with Sia biology is unexpected. Although some of these genes (e.g., Siglecs) are rapidly evolving in all taxa, the frequency of uniquely human changes seems unusually high compared with other species. For example, mouse and rat Siglecs appear nearly identical, and differences among NHHs and other Old World primates seem limited so far (Angata et al., 2004). Secondly, less than 60 genes are known to be directly involved in Sia biology (Altheide et al., 2006). Thus, one biochemical/biological pathway has almost 20% of its genes showing human-specific evolution. Overall, it is reasonable to suggest that Sia biology and Sia-related genes are a "hotspot" for genetic and physiological changes in human evolution. It is parsimonious to assume initially that all of these genetic changes are related to one another, as suggested in the scenario in Fig. 6.1. Although

several aspects are clearly speculative, the scenario is supported by available facts and includes testable concepts and hypotheses.

## METABOLIC INCORPORATION OF Neu5Gc INTO HUMAN CELLS AND A DIETARY SOURCE OF Neu5Gc IN HUMAN TISSUES

We also discovered an unusual nongenetic consequence of *CMAH* loss (Fig. 6.2). Although Neu5Gc was reported in human cancers and fetal samples (suggesting an "oncofetal" antigen) (Malykh et al., 2001), the *CMAH* mutation damages the enzyme's active site (Chou et al., 1998; Irie et al., 1998), which cannot be repaired. Also, a mouse with a human-like

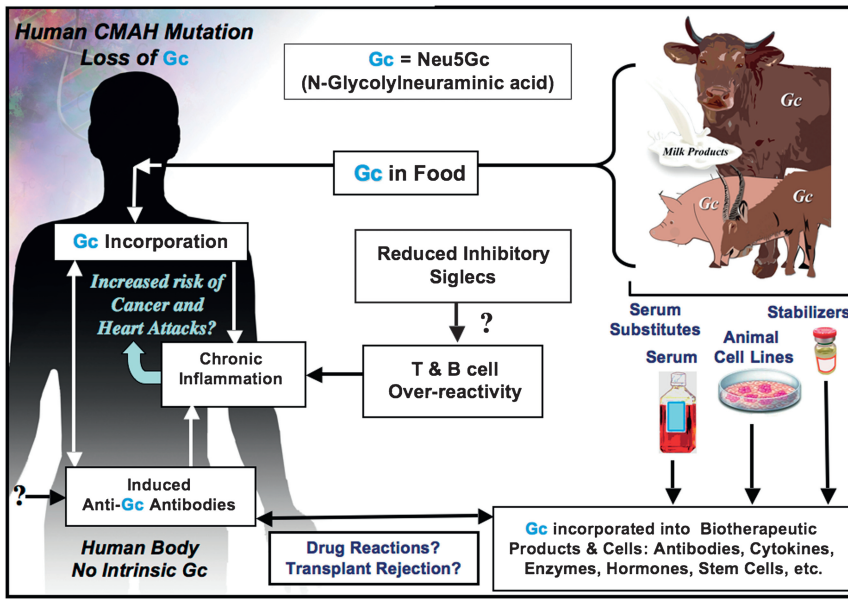



FIGURE 6.2 Two mechanisms for enhanced chronic inflammation and immune reactions in humans. Metabolic incorporation of dietary Neu5Gc (Gc) from mammalian foods in the face of circulating anti-Neu5Gc antibodies may contribute to chronic inflammation in endothelia lining blood vessels and in epithelia lining hollow organs, perhaps contributing to the increased risks of cardiovascular disease and carcinomas associated with these foods. The apparent T- and B-cell overreactivity of humans associated with decreased inhibitory Siglec expression may contribute further toward chronic inflammation. Also shown is that the fact that some molecular and cellular products of biotechnology are likely contaminated with Neu5Gc from multiple sources, potentially contributing to untoward reactions in some individuals.

*Cmah* mutation showed no endogenous Neu5Gc (Hedlund et al., 2007). Absent an alternate pathway for Neu5Gc synthesis, the sugar must enter from external sources. Indeed, cultured human cells express Neu5Gc because of uptake and metabolic incorporation from animal products in the medium (e.g., FCS) (Tangvoranuntakul et al., 2003; Bardor et al., 2005). This process involves macropinocytosis, delivery to the lysosome, and export of free Neu5Gc to the cytosol via the sialin transporter (Bardor et al., 2005). Once Neu5Gc reaches the human cytosol, it is a molecular "Trojan horse." Differing by only one oxygen atom from endogenous Neu5Ac and having been eliminated only recently in evolutionary time, Neu5Gc is handled by human biochemical pathways as if it were native. Indeed, one can feed Neu5Gc to human cells and make them look like NHH cells (Bardor et al., 2005; Nguyen et al., 2005).

Classic studies showed that chickens generate a strong IgY antibody response against Neu5Gc (Malykh et al., 2001). Using a more specific version of such polyclonal antibodies and adding mass spectrometry to be certain (Hedlund et al., 2008), we confirmed the presence of Neu5Gc in human tumors and in fetal tissues (Tangvoranuntakul et al., 2003). Surprisingly, we also found smaller amounts in normal human tissues (Tangvoranuntakul et al., 2003). The likely explanation is a dietary origin. Voluntary Neu5Gc ingestion studies confirmed that humans could indeed take up Neu5Gc (Tangvoranuntakul et al., 2003).

## ANTI-Neu5Gc ANTIBODIES IN HUMANS ARE OF BROAD AND HIGHLY VARIABLE SPECIFICITIES

Why should it matter that human tissues express small amounts of Neu5Gc derived from dietary sources? Although human biochemical pathways do not see Neu5Gc as foreign, it is detected as such by the immune system. Thus, contrary to prior work that used limited methodologies, we find anti-Neu5Gc antibodies circulating in all normal humans. In fact, some individuals have very high levels (Padler-Karavani et al., 2008), including complement-fixing IgGs capable of activating and/or killing cells expressing Neu5Gc (Nguyen et al., 2005). In this situation, a xeno-antigen can become metabolically incorporated into tissues, even while it is detected as being foreign by B cells. Thus, we call Neu5Gc a "xeno-autoantigen" in humans (Pham et al., 2009).

## LIMITED DISTRIBUTION OF Neu5Gc IN FOODS AND DISEASE RISKS ASSOCIATED WITH RED MEAT

Because Sias are not found in plants, and Neu5Gc is not synthesized by microbes, the dietary source of Neu5Gc must be foods of animal

origin. Major sources appear to be red meats (i.e., lamb, pork, and beef) and, to a lesser extent, milk products (Tangvoranuntakul et al., 2003). In contrast, Neu5Gc is not found in poultry, and amounts in fish seem to be low (Tangvoranuntakul et al., 2003). Thus, within limits of current analyses, the primary source of human tissue Neu5Gc appears to be foods of mammalian origin. In this regard, many epidemiological studies have shown an association of red meat ingestion with increased risk for various diseases, including carcinomas (Fraser, 1999; Wiseman, 2008; Sinha et al., 2009), atherosclerosis (Fraser, 1999; Sinha et al., 2009), type-2 diabetes (Song et al., 2004), and age-dependent macular degeneration (Chong et al., 2009). Although there are other theories for how red meat consumption aggravates these diseases, most of these notions (other than the role of saturated fats in atherosclerosis) are unproven. We suggest that metabolic incorporation of dietary Neu5Gc in the face of anti-Neu5Gc antibodies contributes to red meat aggravation of diseases by stimulating chronic inflammation (Hedlund et al., 2008; Pham et al., 2009).

## ANTI-Neu5Gc ANTIBODIES ENHANCE GROWTH OF Neu5Gc-POSITIVE TUMORS IN Neu5Gc-NULL MICE

Human carcinomas efficiently accumulate dietary Neu5Gc for multiple reasons, including up-regulation of lysosomal Sia transport by hypoxia (Yin et al., 2006) and enhanced macropinocytosis caused by growth factor activation. This accumulation occurs in the face of anti-Neu5Gc antibody responses, which are enhanced in such patients (Malykh et al., 2001). This combination suggests an immune reaction insufficient to kill the tumor that may, instead, stimulate it. Indeed, antibody-mediated inflammation is known to facilitate tumor progression by recruiting inflammatory cells, which stimulate angiogenesis and provide growth factors (Tan and Coussens, 2007). We mimicked the human situation using Neu5Gc-null mice bearing a syngeneic mouse tumor line that expresses low levels of Neu5Gc, similar to human tumors. Indeed, passively transferred anti-Neu5Gc immune serum from syngeneic Neu5Gc-null mice increased tumor growth rates associated with inflammation and angiogenesis (Hedlund et al., 2008), and these effects were blocked by a COX-2 inhibitor, a drug type that reduces human tumor incidence (Hedlund et al., 2008). Of course high levels of these antibodies may instead kill tumor cells, and it is possible that persons with very high anti-Neu5Gc antibodies are protected from some cancers. Indeed, can we harness human anti-Neu5Gc antibodies to target human cancers specifically?

## SURPRISING DIFFERENCES BETWEEN HUMAN AND CHIMPANZEE HEART DISEASE

The commonest cause of death in both humans and captive chimpanzees is "heart disease," manifested either as sudden "heart attacks" or as progressive heart failure (Lammey et al., 2008; Varki et al., 2009). However, early case reports suggested that the diseases in humans and chimpanzees are different, and recent studies have confirmed this notion (Lammey et al., 2008; Varki et al., 2009). Chimpanzees and other NHHs develop a progressive fibrotic replacement of the heart muscle (interstitial myocardial fibrosis), which can cause sudden death by altering heart rhythm or slower death by progressive cardiac failure. "Heart disease" in humans is different, caused by deposition of cholesterol in atherosclerotic plaques in the walls of large blood vessels, including coronary arteries (Pham et al., 2009; Varki et al., 2009). This deposition results in sudden or progressive loss of blood supply, explaining the common "heart attack" of humans ("myocardial infarction") or progressive heart failure caused by "ischemic heart disease." Although captive chimpanzees and others NHHs do have atherosclerosis (Varki et al., 2009), myocardial infarction and ischemic heart disease are rare, despite risk factors such as hypertension (Denton et al., 1995) and high levels of LDL cholesterol and lipoprotein(a) (Varki et al., 2009). Why do NHHs not often have the kind of heart disease common in humans? Conversely, why do humans not often suffer from the fibrotic heart disease so common in our closest evolutionary cousins?

## HUMAN-SPECIFIC XENO-AUTOANTIBODY REACTION AGAINST ENDOTHELIUM: A CONTRIBUTING ROLE IN ATHEROSCLEROSIS?

For unclear reasons, accumulation of dietary Neu5Gc in human tissues is not uniform, and it tends to accumulate particularly in epithelial cells lining hollow organs (where carcinomas develop) or in the endothelium lining blood vessels (where atherosclerosis occurs). In fact, cultured endothelial cells fed with Neu5Gc (with Neu5Ac as a negative control) bind anti-Neu5Gc antibodies and deposit complement from human serum, resulting in cellular activation, expression of adhesion molecules, and binding of monocytes (Pham et al., 2009). Thus, although underlying mechanisms exist for many vascular diseases, we suggest that endothelial incorporation of Neu5Gc combines with circulating anti-Neu5Gc antibodies to aggravate processes such as atherosclerosis (Pham et al., 2009). Indeed, human atherosclerotic lesions show Neu5Gc accumulation not just in overlying endothelium but also inside the plaque (Pham et al., 2009). This Neu5Gc accumulation may facilitate production of anti-Neu5Gc

antibodies and further aggravate chronic inflammation in atherosclerosis progression. Thus, this xeno-autoantigen/autoantibody process may be an additional explanation for the increased atherosclerosis risk of consuming red meats and milk products.

## A ROLE FOR Neu5Gc IN RED MEAT-RELATED FOOD POISONING?

Because Neu5Gc is present in some human cells, are we really resistant to Neu5Gc-binding pathogens? The typical low-affinity, high-avidity binding of pathogens to glycans seems unlikely to succeed when Neu5Gc molecules are rare on a human cell surface. An exception may arise when Neu5Gc is targeted by a multivalent toxin with relatively high affinity (Byres et al., 2008). Dietary Neu5Gc loads up epithelial and endothelial cells over time. Subsequent exposure to meat or milk products contaminated with SubAB toxin-expressing *Escherichia coli* would then allow the toxin to bind to gut epithelium, gain access to the bloodstream, and target the kidney endothelium, giving a hemolytic-uremic syndrome (Byres et al., 2008). The process may be facilitated by the fact that (unlike the cows in which this toxin is usually found) humans do not have circulating Neu5Gc-containing glycoproteins to act as natural toxin inhibitors (Byres et al., 2008). Thus, we speculate that individuals who consume large amounts of red meat and milk may not only increase their risk for this type of food poisoning but also prepare their tissues for attack by the toxin (Löfling et al., 2009).

## WAS THE Neu5Gc XENO-AUTOANTIGEN PHENOMENON SIGNIFICANT IN HUMAN EVOLUTION?

Hunting and red meat consumption along with cooking very likely played a supporting role in the emergence of the genus *Homo* (Finch and Stanford, 2004; Carmody and Wrangham, 2009), and milk consumption was positively selected in some human civilizations (Tishkoff et al., 2007b). Indeed, these foods continue to be a vital source of important nutrients for currently undernourished populations. It should be noted that most diseases associated with red meat and/or milk consumption would not have affected natural selection in times past, because they are manifest primarily after the age of peak reproductive fitness. We now live much longer and have much greater access to red meat and milk, thus transforming these once beneficial foods into likely culprits for exacerbating diseases of older humans (Finch and Stanford, 2004).

## POTENTIAL ROLES OF SIA-RELATED CHANGES IN UNIQUELY HUMAN DISEASE PROPENSITIES

We have here discussed multiple potential mechanisms by which uniquely human changes in Sia biology could contribute to such uniquely human disease phenotypes. Although many of the hypotheses are speculative and need further exploration, most are testable either by modeling in Neu5Gc-deficient and/or Siglec-modified mice or by studies in human subjects and human populations. Some of these issues are summarized in Fig. 6.2, along with reference to another area that deserves attention—the contamination of molecular and cellular biotherapeutic products by Neu5Gc derived from nonhuman sources.

## FUTURE DIRECTIONS

This work has generated even more questions than answers. Apart from issues already discussed, some others are briefly discussed below.

### Population Genetics and Polymorphisms of Siglecs

Siglec-12, -14, and -16 are partially pseudogenized (i.e., expressed as active and inactive alleles) in the human population (Angata et al., 2001; Cao et al., 2008; Yamanaka et al., 2009). Do any of these instances represent balanced polymorphisms, and are there more examples? Further studies must address allele distribution in various populations and consider associations with risk of diseases. Additional population-level studies of all Siglecs in NHHs are also warranted, not only to reaffirm that some changes are human specific but also to see whether additional differences and/or polymorphisms exist.

### Siglecs in Bacterial Pathogenesis

Details of how Neu5Ac-expressing pathogens suppress immune responses via inhibitory Siglecs (Carlin et al., 2009b) are as yet unknown. Protein–protein interactions between bacteria and human Siglecs can also mediate similar processes (Carlin et al., 2009a). Meanwhile, the role of the activatory Siglecs in bacterial pathogenesis is postulated to be the opposite, but this notion needs proof. The potential role of Sn in clearing sialylated pathogens also needs further evaluation. We may well be looking at the "tip of the iceberg" regarding roles of Siglecs in bacterial pathogenesis.

### What Is the Fate of Orally Ingested Neu5Gc?

We need to know mechanisms by which Neu5Gc is absorbed from the human gut and delivered to tissues. Early studies in rodents showed that the fate of ingested Neu5Gc may differ, based on the form in which it is presented (Nöhle and Schauer, 1984). We can now study these issues by feeding *Cmah*-null mice different forms of Neu5Gc and looking at its fate in the gut, body fluids, and tissues. At this time, we cannot assume that ingestion of a certain amount of Neu5Gc will deliver a corresponding amount to tissues. A related issue is the fate of Neu5Gc during food processing and cooking.

### Mechanisms of Anti-Neu5Gc Antibody Induction

We are studying the tempo and mode of appearance of these highly variable antibodies in human samples and the potential mechanisms for their induction, using *Cmah*-null mice as a model. We also need to address whether Neu5Gc-containing glycans are truly T-cell-independent antigens, whether the antibody response involves a germline V-set domain, and if the antibody-binding pockets undergo affinity maturation. A related issue is whether these antibodies have any positive value (e.g., potentially protecting against enveloped viruses originating from other species).

### Prognostic Value of Anti-Neu5Gc Antibodies

The highly variable anti-Neu5Gc antibody response of humans is further complicated because Neu5Gc itself is not the entire epitope recognized (i.e., the underlying glycan structures to which it is attached influences binding specificity). Thus, there are many possible Neu5Gc epitopes, and each human has a different response to each of them (Padler-Karavani et al., 2008). Because some of these epitopes are differentially expressed in different tissues, only some of the antibodies may have pathogenic roles, and the antibody subclasses may also make a difference. Perhaps one or more of these anti-Neu5Gc-antibodies will prove to be a predictive, prognostic, or diagnostic marker for one or more diseases. We are pursuing this possibility using a glycan microarray that contains matched Neu5Gc and Neu5Ac glycans as targets.

### Complexity of the "Sialome" in the Cell Surface

The manner in which Sias are presented within the context of a complex cell-surface "landscape" can affect the way they interact with Sia-binding proteins (Cohen et al., 2009). In other words, such proteins recognize not only linear glycan sequences but also more complex structures

presented on "clustered saccharide patches" (Varki, 1994) on cell surfaces, involving glycans of different types (Cohen et al., 2009). Thus, even specific epitopes in glycan arrays may not be representative of the "sialome" at the cell surface. These considerations apply not only to Siglecs but also to anti-Neu5Gc antibody epitopes. Another unexplored issue is whether loss of CMP-Neu5Gc in the Golgi has other consequences for competing biosynthetic pathways (e.g., we found an increase in Sia *O*-acetylation in the *Cmah*-null Neu5Gc-deficient mouse) (Hedlund et al., 2007). Finally, relative differences in biophysical properties between Neu5Gc and Neu5Ac could have consequences. Overall, the Sia biology changes in humans could alter more cell phenomena than we can currently imagine. One approach to exploring this issue is to feed different types of human cells with Neu5Gc (or Neu5Ac as a control) and then study interactions of anti-Neu5Gc antibodies or Siglecs, looking for differential binding by these proteins that cannot be explained by cell-surface glycan sequences.

### Additional Phenotypes of *Cmah*-null Mice

The genomic lesion in our *Cmah*-null mice is almost identical to that of humans (Hedlund et al., 2007). The mice are viable and capable of reproduction, a situation that is not surprising, because the same is true of humans. Further studies of fertility are under way to look for any subtler differences. We have already reported that these mice show delayed wound healing and age-dependent hearing loss, similar to humans (Hedlund et al., 2007). We have preliminary evidence of metabolic differences that also deserve further study. Detailed neurobiological and cognitive studies are required to see if any known differences between human and NHH brains might be manifest. Of course, mice shared a common ancestor with primates more than 60 Mya, and the impact of this biochemical change in a rodent brain may not necessarily reflect what occurred in a hominid ancestor ~2–3 Mya. In this regard, it is fascinating that, even in animals with intact *CMAH* genes, the levels of brain Neu5Gc expression always seem very low (Gottschalk, 1960).

## CONCLUSIONS AND PERSPECTIVES

The fact that so many genes related to Sia biology show human-specific differences from NHHs supports the notion that this system was a "hotspot" for evolutionary changes in the human lineage. Discussed here are some specific ways in which these changes would have impacted the immune system and human pathogen regimes. Although this discussion focuses on current human diseases, it also suggests a role for infectious diseases during human evolution. Of course, Sias and Siglecs are involved

in many other biological pathways. Thus, Sia-related differences between humans and NHHs are worthy of continued investigation.

This Sackler Symposium focused on understanding "The Human Condition" "In the Light of Evolution." Since we reported these genetic differences between humans and NHHs (Chou et al., 1998), many others have been found (Varki and Nelson, 2007; Varki et al., 2008). Any explanation of human evolution and the human condition must take into account all the available data. Indeed, there are many approaches to anthropogeny (explaining the origin of humans) (Varki and Nelson, 2007; Varki et al., 2008), including studies of the fossil and archaeological record since our last common ancestors with other primates; exploring the impact of the environment (biological, physical, and cultural) on humans and other animals; comparisons of the ontogeny of each species; and, of course, species comparisons. All these approaches must be combined in a transdisciplinary manner if we are eventually to explain human origins and human uniqueness.

## ACKNOWLEDGMENTS

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# 7

# Bioenergetics, the Origins of Complexity, and the Ascent of Man

DOUGLAS C. WALLACE

Complex structures are generated and maintained through energy flux. Structures embody information, and biological information is stored in nucleic acids. The progressive increase in biological complexity over geologic time is thus the consequence of the information-generating power of energy flow plus the information-accumulating capacity of DNA, winnowed by natural selection. Consequently, the most important component of the biological environment is energy flow: the availability of calories and their use for growth, survival, and reproduction. Animals can exploit and adapt to available energy resources at three levels. They can evolve different anatomical forms through nuclear DNA (nDNA) mutations permitting exploitation of alternative energy reservoirs, resulting in new species. They can evolve modified bioenergetic physiologies within a species, primarily through the high mutation rate of mitochondrial DNA (mtDNA)–encoded bioenergetic genes, permitting adjustment to regional energetic environments. They can alter the epigenomic regulation of the thousands of dispersed bioenergetic genes via mitochondrially generated high-energy intermediates permitting individual accommodation to short-term environmental energetic fluctuations. Because medicine pertains to a single species, *Homo sapiens*, functional human variation often involves sequence changes in bioenergetic genes, most commonly

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mtDNA mutations, plus changes in the expression of bioenergetic genes mediated by the epigenome. Consequently, common nDNA polymorphisms in anatomical genes may represent only a fraction of the genetic variation associated with the common "complex" diseases, and the ascent of man has been the product of 3.5 billion years of information generation by energy flow, accumulated and preserved in DNA and edited by natural selection.

Charles Darwin and Albert Russel Wallace hypothesized that the environment acts on individual variation via natural selection to create new species (Darwin and Wallace, 1858; Darwin, 1859). However, nothing in the concept of natural selection requires that biological systems should evolve toward ever greater complexity. Yet, throughout the more than 3.5 billion years of biological evolution (Simpson, 2003), life has generated ever more complex forms. What, then, drives increasing biological complexity, and what are its implications for the ascent of man?

## BIOENERGETICS AND THE ORIGIN OF BIOLOGICAL COMPLEXITY

In a thermodynamically isolated system, complex structures decay toward randomness. However, in nonequilibrium systems, the flow of energy through the system generates and sustains structural complexity, and nonhomogeneous structures embody information (Morowitz, 1968; Rubí, 2008).

On Earth, the flux of energy through the biosphere is relatively constant. If the flow of energy were the only factor generating complexity, complexity would soon achieve a steady state between the production and decay of structure. Biology is not static, because the information embedded in biological structures can be encoded and duplicated by informational molecules, DNA and RNA. Therefore, biological complexity increases because a portion of the information generated by energy flow through each generation is added to the accumulated information stores from previous generations. The increasingly complex information can then be used to recreate the more complex structures, as long as there is sufficient energy flow (*Mathematical Formulations*).

The flow of energy through biological structures permits them to reproduce, thus duplicating their DNA. In the process of DNA copying, errors occur. The duplicated mutant DNA changes the physiology and structure of the progeny. These progeny must compete for the available energy resources within the environment. Those that are more effective at acquiring and/or expending the available energy will sustain their

energy flux and thus survive and reproduce. This competition for limited energy resources is the basis of natural selection, which edits the duplicated information based on its efficiency of energy use. Hence, the origin of biological complexity is the interplay between the organizing principle of energy flow, the accumulation of information in nucleic acids, and the winnowing of that information to optimize the use of the available energy flux for information propagation (*Mathematical Formulations*).

During the origin of life, biomolecular systems interacted directly with energy flux, resulting in the formation and polymerization of ribonucleic acids and their subsequent conformational changes to form catalysts to facilitate biochemical reactions (Ricardo and Szostak, 2009). Hence, energy flux was directly linked to the accrual of information within nucleic acids. Subsequently, systems evolved by which the nucleic acid information could be converted into the more flexible proteins permitting more complex structures.

Today, the primary energy source for terrestrial life is the flux of high-energy photons from the Sun through the biosphere. The high-energy photons are collected by plant chloroplasts, descendants of symbiotic cyanobacteria, and the energy used to split water to hydrogen and oxygen. The resulting hydrogen (reducing equivalents) is fixed to carbon to generate glucose. From plant glucose, solar energy flows in the form of reducing equivalents through the biosphere. Animals eat the plants, acquiring the carbohydrates and their stored reducing equivalents. Carbohydrate breakdown products then enter the mitochondria, descendants of symbiotic $\alpha$-protobacteria, and the mitochondria strip the hydrogens off the hydrocarbons and react them with oxygen to generate water, releasing the stored energy (Wallace, 2007).

Therefore, it is the information-generating power of energy flux plus the information storage capacity of nucleic acids, winnowed by natural selection, that continually drives biology to increased complexity. Dobzhansky argued that, "Nothing in biology makes sense except in the light of evolution," but nothing in biology exists without energy flux. Therefore, to understand the origin of species and the ascent of man, we must understand how energy flows through the biosphere, creating the environment; how this energy flow increases biological information; and how the edited information results in complexity and thus man.

## ENERGY AND THE ENVIRONMENT: THREE LEVELS OF BIOENERGETICS

From this analysis, it is clear that the central aspect of an organism's "environment" is energy flow. The energy environment of a biological system is the balance between the energy available to a system and the

demands made on the biological systems' energy supply for survival and reproduction. As life is about the preservation and transmission of information, reproduction is the prime directive.

Organisms within the biosphere interface with energy flux at three levels: (*i*) the source of and requirement for the energy available to a species within its niche, the energy reservoir; (*ii*) the regional differences in energy requirements and availability for subpopulations within a species, the energy environment; and *(iii)* the short-term fluctuations in energy availability and demands made on the individual during life by biological and environmental cycles, the energy fluctuations (Fig. 7.1).

For a species, its energy reservoir is delineated by its food supply and its capacity to survive to reproduce within that niche. In most cases, this requires a specialized anatomy, and anatomical features frequently define species. The switch to new niches as they become available takes animals in the range of tens of thousands to hundreds of thousands of years. So mutations in anatomical genes must accumulate in that time frame to permit speciation. Once the anatomical structures to exploit the energy reservoir are in place, then purifying selection maintains those structures as long as the energy reservoir is stable and can support the species' population. As anatomy is controlled by developmental genes, and as these genes are located on the chromosomes, nuclear DNA (nDNA) mutations are required to create a new species. The time that it takes for the necessary anatomical mutations to accumulate for speciation is determined by the nDNA mutation rate. For multicellular animals, the nDNA gene mutation rate is low, and hence the accumulation of adaptive nDNA mutations is slow.

For different subpopulations of a species, the energy environment can differ due to alternative climatic zones, differences in availability and type of calories, and differing demands on energy resources. These differences can result from migration, climatic change, changes in predation or parasitism, and so forth. Such environmental changes occur over hundreds to thousands of years, and because they are physiological, they require genetic changes in bioenergetic genes.

Bioenergetic genes are distributed throughout the genome and include hundreds to thousands of nDNA-encoded bioenergetic genes plus dozens of mtDNA-encoded bioenergetic genes. The mtDNA bioenergetic genes are the most functionally important because they are central to mitochondrial energy production. The mtDNA genes also have a much higher mutation rate than nDNA genes. Thus, adaptive bioenergetic mtDNA mutations arise in populations within hundreds to thousands of years and permit rapid physiological adaptation to changes in the regional energy environment. As regional subpopulations become established, additional nDNA mutations in bioenergetic genes arise to further solidify the physi-

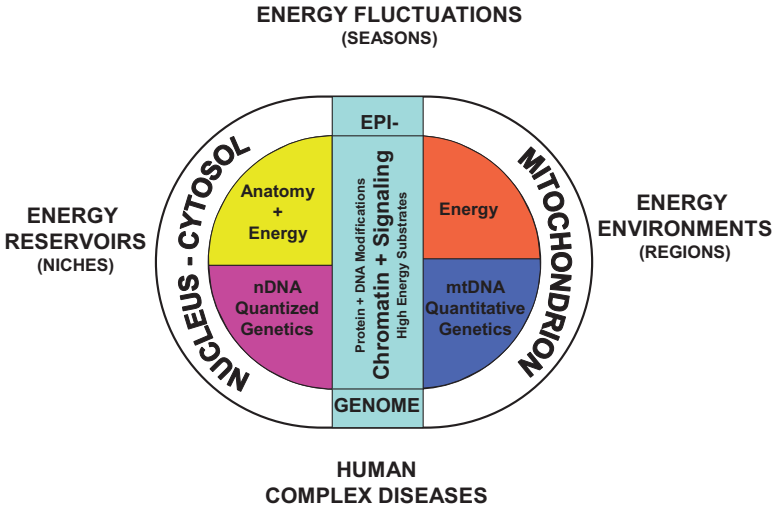


FIGURE 7.1 Three hypothesized levels of eukaryotic animal cell adaptation to energy resources and demands. The primary contributor to the biological environment is the flux of energy through the biosphere. The dichotomy between structure and energy in eukaryotics results from the symbiotic origin of the eukaryotic cell involving the proto-mitochondrion and the proto-nucleus-cytosol. The mitochondrion became specialized in energy production and retained core genes for controlling energy production within the mtDNA. The nuclear-cytosol became specialized in structure with the accrual of the developmental genes in the nDNA. Because growth and reproduction must be coordinated with the availability of energy, the status of the energetic flux through the cellular bioenergetic systems, particularly the mitochondrion, came to be communicated to the nucleus-cytosol by alterations in the nDNA chromatin, the epigenome, and cytosol signal transduction systems, based on the production and availability of high-energy intermediates, reducing equivalents, and ROS produced primarily by the mitochondrion. As a consequence, biological systems interface with the energy environment at three levels: the species level in which nDNA gene variation alters anatomical forms to exploit different environmental energy reservoirs, the species population level in which primarily mtDNA bioenergetic genetic variation permits adaptation to long-term regional differences in the niche energetic environment, and the individual level in which high-energy intermediates reflecting cyclic changes in environmental energetics drive the modification of the epigenome and the signal transduction pathways. [Reproduced with permission from Wallace (2009) (Copyright 2009, Cold Spring Harbor Laboratory Press).]

ological changes (Mishmar et al., 2006; Lane, 2009). Over longer time periods, anatomical mutations can be added, leading toward speciation.

An individual's energy environment fluctuates in cycles throughout its life. These cycles can occur over the individual's life span responding to intra- and intergenerational influences, recur annually in response to seasons, occur monthly relative to the reproductive cycle, or recur daily based on activity and feeding. All of these cyclic changes require reversible alterations in bioenergetic physiology, which cannot be achieved through static genetic changes.

Cyclic changes that occur over tens of years require moderate stability. These are achieved through epigenomic changes: modification of DNA by methylation or of histones through phosphorylation, acetylation, and methylation. Shorter-term reversible changes are accomplished through modulation of transcription factors and alterations in signal transduction pathways. All of these changes must be cued to changes in the energetic environment. Therefore, cyclic changes in the epigenome and signaling pathways are all mediated by changes in the intracellular concentrations of energetic intermediates including ATP for phosphorylation, acetyl-CoA for acetylation, $NAD^+$ for Sirtuin-mediated deacetylation, *S*-adenosylmethionine (SAM) for methylation, oxidation-reduction (redox) state for thiol-disulfide regulation, and reactive oxygen species (ROS) for driving oxidative reactions (Wallace and Fan, 2010).

## ENERGY RESERVOIRS AND SPECIATION

Since the publication of the Darwin–Wallace hypothesis of natural selection, numerous examples have been reported of anatomical changes associated with speciation. The earliest report of anatomical changes associated with exploitation of alternative energy resources was that of Darwin's Galapagos finches, discussed by Darwin and Gould before the Geological Society of London in January 1839. More recently, the change in beak size of these finches has been attributed in part to changes in calmodulin expression (Abzhanov et al., 2006). Comparable studies have continued for more than a hundred years, culminating in the recent report that pelvic loss in stickleback fish is due to deletion of a tissue-specific enhancer of the *Pituitary homeobox transcription factor 1* (*Pitx1*) gene (Chan et al., 2010). Although these studies confirm the importance of anatomical change in speciation, they belie the complexity of the physiological adaptations that are required for a species to occupy a new bioenergetic niche.

## ENERGY ENVIRONMENTS AND SUBPOPULATION RADIATION

To understand the radiation of subpopulations of a species, it is necessary to study the intraspecific variation of a single species that occupies a wide range of regional energetic environments. The best studied species in this regard is *Homo sapiens.*

A striking feature of the radiation of mammalian and primate genomic elements is that mtDNA sequences show a much greater sequence evolution rate than do nDNA sequences (Brown et al., 1982; Neckelmann et al., 1987; Wallace et al., 1987). This rapid mtDNA radiation is reflected in the high degree of functional and regional variation of human mtDNAs (Wallace et al., 2007). The mtDNA genes of all animals encode the core proteins of OXPHOS, so mtDNA mutations directly affect bioenergetic physiology and provide the ideal genetic system for adaptation to changes in regional energy environments.

### Mitochondrial Bioenergetics and the mtDNA

The unique capacity of the mtDNA to regulate bioenergetics has its roots in the symbiotic origin of the eukaryotic cell. Current theory postulates that a glycolytic motile microorganism, the proto-nucleus-cytosol, formed an association with an oxidative α-protobacterium, the proto-mitochondrion, about 2 billion years ago, probably in response to the rise in atmospheric oxygen generated by free-living cyanobacteria.

As the symbiosis matured, the two organisms consolidated their metabolic pathways and exchanged genes, natural selection enriching for more efficient forms. During the ensuing intersymbiont reorganization, most of the genes of the mitochondrial genome were transferred to the nDNA to become interspersed among the existing nuclear-cytosol bioenergetic genes. Ultimately, one genetic and metabolic combination was sufficiently energetically efficient to permit the advent of multicellularity. In this proto-multicellular eukaryote, 98% of the protein-coding genes of the mitochondrial genome had been transferred to the nucleus, encompassing all of the polypeptide genes for mitochondrial growth, reproduction, and metabolism plus ≈80 polypeptide genes for OXPHOS (Wallace, 2005, 2007; Wallace et al., 2010).

The mtDNAs of multicellular animals all retained roughly the same 13 OXPHOS polypeptide genes. These include seven (ND1, 2, 3, 4L, 4, 5, and 6) of the 45 subunits of OXPHOS complex I, one [cytochrome *b* (cytb)] of the 11 subunits of complex III, three (COI, II, and III) of the 13 subunits of complex IV, and two (ATP 6 and 8) of the ≈16 subunits of complex V. Animal mtDNAs also retain the rRNA and tRNA genes for mitochondrial protein synthesis and a control region for regulating mtDNA replication and transcription (Wallace, 2005, 2007; Wallace et al., 2010).

Carbohydrates and fats are metabolized through the mitochondrial intermediate acetyl-CoA, by the tricarboxylic acid (TCA) cycle and β-oxidation pathways. These pathways strip the reducing equivalents off of the hydrocarbons and transfer them to mitochondrial $NAD^+$ and FAD. The resulting reducing equivalents (electrons) are transferred from NADH + $H^+$ and $FADH_2$ to complexes I and II, respectively, initiating the electron transport chain (ETC). From complexes I and II, the electrons are transferred to coenzyme Q (CoQ) and then through complex III, cytochrome *c*, and complex IV to reduce $1/2\ O_2$ into $H_2O$. The energy that is released as the electrons pass through complexes I, III, and IV is used to transport protons out across the mitochondrial inner membrane to generate a trans-inner membrane electrochemical potential ($\Delta P = \Delta\psi + \Delta\mu^{H+}$). The energy stored in this capacitance, $\Delta P$, can then be used by the ATP synthase, complex V, to condense ADP + Pi to ATP, the ATP being exported to the cytosol by the adenine nucleotide translocators (ANTs). $\Delta P$ can also be used to drive many other functions including the import of cytosolic $Ca^{2+}$ into the mitochondrial matrix (Wallace, 2005, 2007; Wallace et al., 2010).

If excess electrons accumulate in complexes I and III and CoQ, they can be donated directly to $O_2$ to give superoxide anion ($O_2^{\cdot -}$), a potent oxidizing agent. Mitochondrial $O_2^{\cdot -}$ can be converted to hydrogen peroxide ($H_2O_2$) by the matrix Mn superoxide dismutase (MnSOD) or the intermembrane space Cu/ZnSOD. The $H_2O_2$ can acquire an additional electron, producing the highly reactive hydroxyl radical (·OH), or can be reduced to water by glutathione peroxidase. Consequently, the core ROS species ($O_2^{\cdot -}$, $H_2O_2$, and ·OH) are primarily of mitochondrial origin (Wallace, 2005, 2007; Wallace et al., 2010).

The mitochondrion also incorporates a self-destruct system, the mitochondrial permeability transition pore (mtPTP). The mtPTP can be activated by a decline in either $\Delta P$ or high-energy phosphates or an increase in mitochondrial matrix $Ca^{2+}$ level or ROS toxicity.

The efficiency by which OXPHOS generates ATP is called the coupling efficiency. This is determined by the efficiency with which complexes I, III, and IV convert the oxidation of reducing equivalents into $\Delta P$ and the efficiency by which complex V converts $\Delta P$ into ATP. A tightly coupled OXPHOS system maximizes ATP generation per calorie burned. A less coupled system must burn more calories for the same amount of ATP, resulting in a higher caloric intake and greater heat production (Wallace, 2007).

All of the proton translocating complexes of OXPHOS (complexes I, III, IV, and V) must be balanced to ensure that one complex is not disproportionately permeable to protons and thus shorts $\Delta P$. This is achieved by having the core electron and proton transport genes retained on a single piece of nonrecombining DNA, the exclusively maternally inher-

ited mtDNA. This requires that each new mutation be tested by natural selection in the context of the previously existing variants encoded by that mtDNA (Wallace, 2007).

**mtDNA Variation in Adaptation and Disease**

Because each cell has hundreds of mitochondria and thousands mtDNAs, new mtDNA mutations generate an intracellular mixture of mutant and normal mtDNAs, heteroplasmy. The percentage of mutant and normal mtDNAs can be unequally distributed at cytokinesis, such that the percentage of mutant mtDNAs can drift during successive mitotic and meiotic cell divisions, replicative segregation.

As the percentage of deleterious mtDNA mutations increases, the energy output of the cell declines until it drops below the minimum energy output required for that cell type to function and symptoms ensue, the bioenergetic threshold. To date, more than 200 pathogenic mtDNA mutations have been identified, and these cause all of the symptoms seen in the common metabolic and degenerative diseases including diabetes and metabolic syndrome, forms of blindness, deafness, neurodegenerative disease, myopathy, cardiomyopathy, renal dysfunction, and hepatic failure. Mutations in the mtDNA also contribute to cancer and aging (Wallace, 2005, 2007).

The high mtDNA mutation rate means that deleterious mtDNA mutations are very common. The frequency of recognized mitochondrial diseases is already estimated at 1/4,000–1/5,000 (Schaefer et al., 2008), and the de novo mtDNA mutation rate observed in cord blood, as assessed through 15 known pathogenic mutations, has been reported as 1 in 200 (Elliott et al., 2008). Given the high mtDNA mutation rate and the great importance and conservation of the mtDNA genes, the cumulative mtDNA genetic load should drive animal species to extinction. This paradox is resolved because the mammalian ovary encompasses a selective system that systematically eliminates those proto-oocyes that harbor the most severely deleterious mtDNA mutations (Fan et al., 2008; Stewart et al., 2008). Consequently, only oocytes with mildly deleterious, neutral, or beneficial mtDNA variants are ovulated and can be transmitted into the next generation. New mtDNA variants are constantly being introduced into animal populations, thus modifying individual energy metabolism. These variants provide the physiological variability required for subpopulations to adjust to new regional energetic environments.

As an mtDNA harboring an adaptive mutation becomes enriched in a new energy environment, additional neutral or advantageous mtDNA mutations accumulate sequentially along that regional maternal lineage. This creates distinctive branches of the mtDNA tree, each a cluster of

related mtDNA haplotypes known as a haplogroup. Because the number of possible adaptive mtDNA mutations is finite, the same adaptive mutations have been observed repeatedly on different mtDNA backgrounds around the world. This convergent evolution confirms that these mtDNA mutations are adaptive.

Each regional indigenous human population has its own distinctive mtDNAs. African mtDNAs belong to macrohaplogroup L, which encompasses the greatest mtDNA sequence diversity, implying an African origin for the mtDNA tree (Johnson et al., 1983; Cann et al., 1987; Merriwether et al., 1991). Of all of the African mtDNA variants, only two mtDNAs successfully left Africa and colonized Eurasia, founding macrohaplogroups M and N. Only macrohaplogroup N radiated into Europe, generating the European-specific lineages H, I, J, Uk, T, U, V, W, and X. Both macrohaplogroups M and N radiated into Asia, generating a plethora of mtDNA lineages. Of these, only A, C, and D became enriched in northeastern Siberia and were in a position to cross the Bering land bridge to colonize the Americas (Wallace, 2007; Wallace et al., 2007).

The regional specificity of mtDNA lineages suggests that mtDNA variation permitted humans to live in different climatic zones, perhaps through regulation of OXPHOS coupling efficiency and thus thermal regulation (Wallace, 2007). Accordingly, mtDNA variation but not nDNA variation correlates with regional temperature extremes (Balloux et al., 2009). In mtDNAs harboring the two founder macrohaplogroup N missense mutations, ND3 nucleotide 10398 (amino acid change A114T) and ATP6 nucleotide 8701 (amino acid change A59T), several mitochondrial physiological parameters have been shown to be altered (Kazuno et al., 2006). Furthermore, a mtDNA control region variant has been found to change mitochondrial transcription and copy number (Suissa et al., 2009).

Although mild mtDNA mutations may be adaptive in one local energy environment, the same mutation might be maladaptive in another energy environment. Consistent with this conjecture, mtDNA haplogroups have been found to be important risk factors for a wide range of common metabolic and degenerative diseases and to influence various cancers and longevity (Wallace, 2005; Wallace and Fan, 2009).

Once a subpopulation has become established in a region through adaptive mtDNA mutations, additional mutations can arise in nDNA bioenergetic genes to further enhance physiological adaptation and contribute to speciation (Mishmar et al., 2006). Examples of such variants in human populations include polymorphisms in the nDNA-encoded mitochondrial uncoupling protein genes (Bulotta et al., 2005; Cha et al., 2006; Nakano et al., 2006; Villarroya et al., 2006) and in the bioenergetic transcription factor genes for the peroxisome-proliferator-activated receptor γ (PPARγ) (Altshuler et al., 2000) and PPARγ-coactivator 1α (PCG-1α)

(Ek et al., 2001; Muller et al., 2003). These polymorphic genes have also been found to be risk factors for obesity and diabetes in certain populations. In large-scale population studies that cut across regional energy environments, the associations with PPARγ and PGC-1α are lost (Diabetes Genetics Initiative of Broad Institute of Harvard and MIT et al., 2007; Scott et al., 2007; Sladek et al., 2007; Zeggini et al., 2007). This paradox may result from the mixing of populations from different energy environments which harbor alternative region-specific adaptive genetic variants, such that the impact of each individual regional variant is averaged out.

## ENERGY FLUCTUATION AND CYCLIC ADAPTATION

Individual adjustments to cyclic changes in the energy environment must be reversible. Therefore, cyclic changes cannot be due to DNA sequence changes, but must be due to changes in bioenergetic gene expression. Relevant cyclic bioenergetic changes encompass a wide temporal range from intergenerational effects to daily fluctuations. The more long-term cyclic modulations occur as epigenomic changes at the chromatin level, whereas the shorter-term changes involve alterations of transcription factors, signal transduction pathways, and protein activation.

### Epigenomic Regulation of Bioenergetics

Because the primary environmental variable is energetics, and because the bioenergetic genes are dispersed across the chromosomes and mtDNA, responses to environmental fluctuation must involve pan genomic regulation of bioenergetic genes. The modulation of the epigenome by intracellular concentrations of high-energy intermediates provides the necessary link between the energetic state of the environment and the modulation of cellular gene expression. When calories are abundant, the organism must grow and reproduce, which requires the up-regulation of gene expression. When calories are limiting, the organism must become quiescent, requiring the shutdown of gene expression (Wallace and Fan, 2010).

Epigenomic regulation occurs at the chromatin level. The nDNA is packaged in nucleosomes encompassing 146–147 base pairs of DNA wrapped around a complex of two copies each of histones H2A, H2B, H3, and H4. The amino-terminal tails of the histones are positively charged, such that they bind electrostatically to the phosphate backbone of the DNA and inhibit transcription. However, when the histone tails become phosphorylated by kinases using ATP, or acetylated by histone acetyltransferases (HAT) using acetyl-CoA, the positive charges are neutralized, the affinity of the histone tails to DNA is reduced, and the chromatin opens to permit transcription. Methylation of DNA and of histone tails by

methyltransferases using SAM can also modulate the affinity of proteins for DNA.

ATP is generated by both glycolysis and OXPHOS when caloric reducing equivalents are prevalent. Mammalian cell acetyl-CoA is generated primarily in the mitochondrion during pryruvate or fatty acid oxidation. Within the mitochondrion, the acetyl-CoA is converted to citrate by condensation with oxaloacetate (OAA) via citrate synthetase. Citrate can be exported into the cytosol, where it is cleaved back to acetyl-CoA and OAA by ATP-citrate lyase (Wallace and Fan, 2010). Mitochondrial acetyl-CoA can also be exported out of the mitochondrion as acetylcarnitine by the carnitine/acylcarnitine acetyltranslocase. In the cytosol, acetylcarnitine reverts back into acetyl-CoA for use in histone acetylation (Madiraju et al., 2009).

SAM is produced in the cytosol by the reaction L-methionine + ATP. ATP is generated by the mitochondrion and glycolysis, whereas the methyl groups to convert homocystine to methionine come from the mitochondrion. Therefore, all of the primary substrates for chromatin modification are produced by the bioenergetic pathways, which in turn are fueled by the availability of calories in the environment (Wallace and Fan, 2010).

Evidence that the epigenome regulates bioenergetics comes from the facts that pathogenic mtDNA mutations result in symptoms similar to those attributed to the epigenomic disease and that several epigenomic diseases have been associated with mitochondrial dysfunction. Epigenomic diseases affect imprinting, methylation, and chromatin organization (Feinberg, 2007). The epigenome can regulate dispersed bioenergetic genes in either the *cis* configuration for adjacent genes or in the *trans* configuration for dispersed genes. Current knowledge about chromatin organization suggests that the *cis* regulation occurs with chromatin loop domains and that *trans* regulation occurs by diffusible *trans*-acting factors or by bringing together dispersed genes into transcriptional islands, in part through shared enhancer sequences (Wallace and Fan, 2010).

Imprinting diseases generally involve *cis*-acting epigenetic defects. In Angelman and Prader-Willi syndromes, the perturbation of cell function involves genetic inactivation of the active allele on chromosome 15q11–13 in the context of an inactive imprinted allele on the opposite chromosome. The pathophysiology of Angelman syndrome appears to be mitochondrial, as analysis of an Angelman murine model has revealed that the hippocampal neurons have a reduced synaptic vesicle density and shrunken mitochondria and the brain has a partial defect in OXPHOS complexes II + III (Wallace and Fan, 2010).

The pathophysiology of Beckwith-Wiedemann syndrome and Wilm's tumor may also involve bioenergetic dysfunction. Both of these diseases are associated with loss of imprinting (LOI) on chromosome 11q15.5

within a chromatin loop domain encompassing the insulin-like growth factor 2 (*IGF2*) gene. IGF2 may act through the PI3K-Akt-FOXO pathway to modulate energy metabolism (Feinberg, 2007; Wallace and Fan, 2010).

Rett syndrome and the laminopathies may be epigenomic diseases that act in *trans* to affect mitochondrial function. Rett syndrome is caused by mutations in the methyl-CpG binding protein 2 *(MeCP2)*, which binds to $^{me}$CpG islands throughout the chromosomes (Loat et al., 2008). As abnormal mitochondria and mitochondrial function have been reported in several Rett patient studies, loss of MeCP2 might disrupt the coordinate regulation of nDNA energy gene expression (Wallace and Fan, 2010). The laminopathies are caused by mutations in the laminin A/C gene *(LMNA)*, which disrupt the nuclear architecture and potentially transcriptional islands. Mutations in the *LMNA* gene have been found to produce similar phenotypes to those found in mtDNA mutations and a study of cells harboring *LMNA* mutations revealed mitochondrial defects. Therefore, various epigenomic defects may affect mitochondrial function, implying that an important function of the epigenome is to coordinate the expression of the dispersed bioenergetic genes (Wallace and Fan, 2010).

**Bioenergetic Regulation of Signal Transduction and Metabolism**

To respond to more rapid energy environment fluctuations, animal cells modify transcription factors and signal transduction systems via high-energy intermediates. High and low blood sugar results in the secretion of insulin by the pancreatic β cells and glucagon by the pancreatic α cells, respectively. Insulin binds to the insulin receptor, which signals, through phosphatidylinositol-3-kinase (PI3K) and Akt/PKB, to phosphorylate and inactivate the FOXO transcription factor. When not phosphorylated, FOXO binds to the PCG-1α promoter and increases PGC-1α expression, which up-regulates mitochondrial biogenesis and OXPHOS. Thus, in the presence of glucose, FOXO is inactivated, OXPHOS is down-regulated, and glycolysis is favored. In the absence of glucose FOXO is active and OXPHOS is up-regulated to burn fat. Similarly, glucacon binds to the glucagon receptor to activate adenylylcyclase, and the resulting cAMP activates protein kinase A (PKA) to phosphorylate CREB. Activated CREB also binds to the PGC-1α promoter and up-regulates OXPHOS. Low glucose thus doubly induces OXPHOS by inhibiting insulin signaling and enhancing glucagon signaling (Wallace, 2007).

The PI3K pathway is also linked via the tuberous sclerosis protein complex (TSC) to the mTORC1 regulation of nutrient metabolism; mTORC1 is also modulated by AMP kinase, which is activated by reductions in high-energy phosphates. Virtually every signal transduction pathway is modulated by ATP-mediated phosphorylation, so almost all cellular

processes are regulated by the availability of high-energy intermediates (Wallace and Fan, 2010; Wallace et al., 2010).

Changes in cellular redox state are also important in regulating transcription factors and metabolic pathways. The redox state of the cell reflects the flux of reducing equivalents from the mitochondrion, through the nucleus-cytosol, and on to the other cellular compartments. Reducing equivalents enter the mitochondrion as NADH + $H^+$ at −250 mV and flow through the ETC and other cellular pathways down to oxygen at +800 mV. The importance of the subcellular redox status is illustrated by the class III histone deacetylase Sirt1. Sirt1 removes acetyl groups from proteins in the presence of $NAD^+$ via the reaction: acetyl-lysine + $NAD^+$ → lysine + nicotinamide + 2′-*O*-acetyl-ADP ribose. Although the oxidized $NAD^+$ is a required coreactant, the reduced form of $NAD^+$, NADH + $H^+$, cannot be used by Sirt1. Therefore, deacetylation is coupled to the cellular redox state. The FOXO and PGC-1αtranscription factors are inactivated by acetyl-CoA-mediated acetylation. They can be reactivated by deacetylation by Sirt1 + $NAD^+$. When glucose is abundant, glycolysis reduces cytosolic $NAD^+$ to NADH + $H^+$ in the process of generating pyruvate. The pyruvate is converted to acetyl-CoA in the mitochondrion, and the acetyl-CoA is exported back into the cytosol, and is used to acetylate and inactivate PGC-1α and FOXO. Because the cytosolic $NAD^+$ is reduced to NADH + $H^+$, Sirt1 cannot deacetylate FOXO and PGC-1α, and OXPHOS is inhibited whereas glycolysis is favored. By contrast, when fatty acids and ketone bodies (acetoacetate and β-hydroxybutyrate) are metabolized, they are burned entirely within the mitochondrion, and the cytosolic $NAD^+$ remains oxidized. The combination of Sirt1 + $NAD^+$ then deacetylates and activates the FOXO and PGC-1α transcription factors, up-regulating OXPHOS to oxidize fats and ketones (Wallace, 2009).

The redox regulation of cellular metabolism goes far beyond its effects in Sirt1 activity. In the mitochondrion, a substantial portion of the NADH is oxidized via the ETC using $O_2$ to generate $\Delta P$, but the redox state of a portion of the NADH + $H^+$ is increased by the nicotinamide nucleoside transhydrogenase (Nnt), using energy from $\Delta P$ to drive the transfer of reducing equivalents from NADH + $H^+$ to NADPH + $H^+$ with a redox potential of −405 mV. Mitochondrial NADPH + $H^+$ can then drive the reduction of oxidized glutathione (GS-SG) to reduced glutathione (2GSH), and GSH can act through the glutathione peroxidases to detoxify mitochondrial ROS and other radicals. NADPH + $H^+$ also provides reducing equivalents for mitochondrial thioredoxin-2$(SH)_2$/SS [Trx2$(SH)_2$/SS], to drive peroxidoxins to reduce radical species and to mediate the modulation of the redox status of thiol-disulfides of an array of mitochondrial enzymes directly regulating their activity (Kemp et al., 2008; Wallace et al., 2010).

To a limited extent, the reducing equivalents of mitochondrial NADH + $H^+$ and NADPH + $H^+$ can also be transferred to the cytosol. Reducing equivalents from NADH + $H^+$ can be exported via the mitochondrial inner membrane aspartate–malate shuttle. Mitochondrial NADPH + $H^+$ can be exported to the cytosol via citrate, which is converted to malate. Malate is then oxidized by the cytosolic malic enzyme to pyruvate in association with the reduction of $NADP^+$ to NADPH + $H^+$. Cytosolic NADPH + $H^+$ can also be generated by glucose 6-phosphate dehydrogenase (Wallace et al., 2010).

The cytosolic NADPH + $H^+$ redox state is approximately –393 mV. This can drive cytosolic glutathione reductase and associated glutathione peroxidases to buffer cytosolic ROS and the glutaredoxins to regulate the redox status of proteins. Cytosolic NADPH + $H^+$ also determines the redox status of the cytosolic and nuclear thioredoxin-1$(SH)_2$/SS [Trx1$(SH)_2$/SS]. Trx1$(SH)_2$/SS donates reducing equivalents to cytosolic peroxidoxins to control radicals, and to the thiol/disulfides of enzymes and transcription factors to regulate their activity. Trx1$(SH)_2$/SS directly regulates proteins such as Oct-4, but also regulates the redox status of the bifunctional apurinic/apyrimidinic endonuclease/redox factor-1(APE/Ref1$^{Red/Ox}$). The redox state of APE/Ref1$^{Red/Ox}$, in turn, modulates the activity of a variety of transcription factors including activator protein-1 (AP1, c-Jun), NF-E2–related factor–2 (Nrf2), NF-κB, p53, glucocorticoid receptor (GR), estrogen receptor (ER), and hypoxia-inducible factor-1α (HIF-1α) (Kemp et al., 2008; Wallace et al., 2010).

Mitochondrially modulated ROS production also regulates the activity of a wide spectrum of enzymes, including tyrosine and serine/threonine kinases, multiple phosphatases, and NF-κB–mediated cytokine and inflammatory responses (Wallace et al., 2010). ROS levels as well as oxygen tension directly regulate the activation of the HIF-1α transcription factor. HIF-1α is constitutively synthesized but is inactivated in the presence of high $O_2$ by hydroxylation via prolyl hydroxylase domain protein 2 (PHD2). Reduced $O_2$ and mitochondrially generated ROS production can inhibit PHD2 activity, stabilizing HIF-1α. HIF-1α together with HIF-1αthen act as a transcription factor to induce the expression of glycolytic enzymes and vascularization and hematopoietic factors, alter the oxygen affinity of OXPHOS complex IV by inducing subunit COX4-2 and the mitochondrial LON protease to degrade subunit COX4-1, induce pyruvate dehydrogenase (PDH) kinase 1 to inhibit PDH, and thus block the conversion of pyruvate to acetyl-CoA, induce MXI-1 to inhibit Myc, thus reducing expression of PGC-1α, and induce BNIP3 to initiate the autophagic degradation of the mitochondria (Semenza, 2008; Wallace et al., 2010). Hence, energy flux through the animal cell regulates virtually every aspect of cellular growth, differentiation, quiescence, and death.

## BIOENERGETICS AND THE ASCENT OF MAN

This energetic-information hypothesis on the origin of biological complexity has fundamental implications for the ascent of man. Since Vesalius' anatomical catalog published over 450 years ago, Western medicine has taken a predominantly anatomical perspective of medicine, the anatomical paradigm of disease. Similarly, since the discovery of the Mendelian laws of inheritance about 150 years ago, it has been assumed that all genes are inherited in a Mendelian fashion, the Mendelian paradigm of genetics. Since all anatomical genes are chromosomal and thus also Mendelian, these two paradigms provided an internally consistent perspective on biology and medicine for 100 years. The anatomical and Mendelian paradigms of medicine have produced many advances, such as understanding the molecular basis of diseases resulting from severely deleterious nDNA mutations in structural genes. Because of these successes, it has been assumed that if a disease Mendelizes, it is genetic, and if it does not, it is "complex," the latter implying an interaction between multiple Mendelian genes plus the environment.

Medicine pertains exclusively to humans, a single species. Consequently, the most important variables in intraspecific adaptation to local environmental changes, which are primarily energetic, should be alterations in bioenergetic genes, either genetic or epigenetic. Mutations in the mtDNA are more common than nDNA mutations and epigenomic changes can rapidly change the expression of bioenergetic genes. Efforts to explain common "complex" diseases like diabetes based exclusively on the analysis of nDNA variation in tissue-specific genes would then be expected to be relatively unproductive, as has been the case. In reality, common diseases may not be particularly "complex"; they may simply be energetic and non-Mendelian.

The discovery that the mammalian ovary harbors a selective system to eliminate the most deleterious mtDNA mutations explains why the high mtDNA mutation rate does not drive mammalian populations to extinction from overwhelming mtDNA genetic load. Since the mtDNA only encodes OXPHOS genes and OXPHOS genes are expressed in every cell of the body, intraovarian selection can monitor the physiological consequences of mitochondrial OXPHOS defects within proto-oocytes and eliminate those with the most severe bioenergetic aberrations.

By contrast, most nDNA-encoded developmental genes are not expressed in the gametes, so gametes harboring severely deleterious developmental mutations cannot be phenotypically identified and eliminated within the gonads. Purifying selection of deleterious nDNA mutations must occur postconception, at the individual organism level. This greatly increases the genetic load and energy wastage caused by deleterious nDNA mutations. To avoid introduction of too many deleterious

nDNA mutations into the population, the nDNA mutation rate must be kept low. Still, the nDNA mutation rate cannot be zero, as maintaining this level of fidelity would be too energy expensive and would also eliminate the capacity of organisms to adapt to new energy reservoirs. Genetic load then places an upper limit on the combination of the nDNA mutation rate and the genetic target size, the amount of protein coding information in the organism's genome. In animal species, a steady state may have been achieved between nDNA mutation rate and gene target size when the genome complexity reached that of the invertebrates. This may explain why the number of protein coding genes is similar between *Caenorhabditis elegans*, *Drosophila melanogaster*, *Mus musculus*, and *Homo sapiens*, and that most of the increased structural complexity in vertebrates has been achieved by alternative splicing and elaboration of complex temporal and spatial gene regulation. Because of these nDNA constraints and the direct interface between organismal bioenergetics and changes in the energetic environment, the dominant mechanism for intraspecific adaptation to environmental change occurs through bioenergetics.

Although there may be an upper limit on the amount of structural gene information that can be added to the nuclear genomes of higher animals, the flux of energy through the biosphere is continually adding information to the environment. Much of this physical and biological information is too transient to be of value to future animal generations and thus is not stored in DNA. The present position of food resources would be an example of such information. Still, this information is of benefit for the survival and reproduction of the individual. As a result, the continued evolution of information storage and retrieval systems needed to shift from the use of DNA to store the information to the use of DNA to build structures that could store transient information. These short-term information storage and retrieval systems ultimately became the brain.

The brain's information is lost when the individual dies. Yet, some of this information may be beneficial to the individual's relatives and descendants, requiring that this information be transmitted between related individuals. This provided the impetus for the evolution of language and learning, leading to culture, libraries, and computers.

Toward the end of their lives, Darwin and Wallace became estranged. Darwin argued that natural selection was sufficient to explain the origin of the existing biological world. Wallace believed that natural selection alone was insufficient to explain the existence of complex structures such as the human brain. From the bioenergetic perspective, Wallace's reservations were justified, as complexity can be generated only through the information-generating power of energy flow and the cumulative information storage capacity of nucleic acids. It took more than 3.5 billion years for these systems to amass sufficient information to generate the human brain.

Thus the missing concept that Wallace sought to explain the ascent of man is the interaction between energetics and information.

## MATHEMATICAL FORMULATIONS

According to the second law of thermodynamics, an energetically isolated system will move toward equilibrium in association with increased disorder or entropy ($S$), $\Delta A = \Delta U - T\Delta S$, where $A$ is Helmholtz free energy (energy for useful work), $U$ is the total energy of the system, and $T$ is the absolute temperature. In a system in which $T$ is constant, disorder increases ($\Delta S$ is +) as $\Delta A$ declines, provided $U$ is constant. However, in a system where energy flows through the system, such that an equal quantity of energy enters and leaves the system, the total instantaneous energy ($U$) remains constant but the energy to perform work ($\Delta A$) and thus produce change is increased. If $\Delta A$ becomes greater than $U$, then $\Delta S$ becomes –, disorder decreases, and the system becomes more ordered, which is the case for biological systems.

With sufficient information ($I$), any system can be described. The greater the disorder of a system (larger the $S$) the greater the information that is necessary for its description, $S = k_i I$, were $I$ is information and $k_i$ is a constant. However, energy flow generates structure, the nature of which is determined by the inherent properties of the system. To describe a system requires the information to describe the physical properties of the system, $I(p)$, and the information inherent in the system that permits the creation of the ordered aspects of the system, $I(o)$. By analogy, to describe a glass of ice water requires information about the physical properties of the ice and water but also information about the inherent properties of $H_2O$ that cause dipole interactions and crystalline lattice formation.

The information to describe the entire system is related to the energy of the entire system, $U$, and encompasses both the physical $[I(p)_u]$ and ordering $[I(o)_u]$ components of the system's information. Therefore, $U = k_1 I(p)_u + k_2 I(o)_u$ and the information embodied in $U$ is $I(u) = I(p)_u + I(o)_u$. By analogy, $A = k_3 I(p)_a + k_4 I(o)_a$ and the information embodied in $A$ is $I(a) = I(p)_a + I(o)_a$. In a physically isolated system, the usable information in $A$, $I(a)$, is less than that in $U$, $I(u)$, and the information content of the system decays. To maintain a steady-state structure, additional energy must be added to $A$, through energy flux (Ef). This flow of energy will generate information through interaction with the components of the system, $\text{Ef} = k_5 I(\text{ef})$. This information is then added to the usable information of the system, $I(a) = I(p)_a + I(o)_a + I(\text{ef})$. Therefore, $S = ([k_1 I(p)_u + k_2 I(o)_u] - [k_3 I(p)_a + k_4 I(o)_a + k_5 I(\text{ef})])/T$.

If the system is to avoid decay, Ef must generate information, $I(\text{ef})$, that is equal to or greater than the difference between $I(u)$ and $I(a)$. In a

complex system that does not decay ($\Delta S$ is zero or negative), $A = k_3I(p)_a + k_4I(o)_a + k_5I(\text{ef}) \geq k_1I(p)_u + k_2I(o)_u = U$. Consequently, if $k_5I(\text{ef}) > [k_1I(p)_u + k_2I(o)_u] - [k_3I(p)_a + k_4I(o)_a]$, then information and order increase within the system.

Because the flux of energy across the Earth's surface, Ef, is roughly constant, the amount of organizing information from Ef must also be constant. Hence, if this were the only factor, the biosphere would quickly come to stasis. The reason that this does not occur is because information pertaining to the ordering of the system, $I(o)$, can be accumulated, using an appropriate information storage and retrieval system. In biology, this information storage system is nucleic acids, $I(\text{na})$. Therefore, in the biosphere a portion of $I(\text{ef})$, $I(o)_u$, and $I(\text{o})_a$ are retained as $I$ (na): $I(\text{ef})_{\text{na}}$, $I(o)_{\text{na}(u)}$, and $I(o)_{\text{na}(a)}$. Hence, $I(\text{ef})_{\text{na}} + I(o)_{\text{na}(a)}$ must be $> I(o)_{\text{na}(u)}$ for the biosphere to continually increase in complexity.

The nucleic acid information present in the biosphere today, $I(\text{na})$, is the sum of the total nucleic acid information that has formed over 3.5 billion years of terrestrial biology, $I(\text{na})_t$, minus that portion of the total information that has been removed by natural selection or cataclysm, $I(\text{na})_e$. $I(\text{na}) = I(\text{na})_t - I(\text{na})_e$. The nucleic acid information in today's biosphere, $I(\text{na})$, divided by the sum of the energy flux through the biosphere over the past 3.5 billion years, represents the average efficiency by which energy flux has been converted into conserved biological information on Earth.

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# 8
# Genome-wide Patterns of Population Structure and Admixture Among Hispanic/Latino Populations

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Hispanic/Latino populations possess a complex genetic structure that reflects recent admixture among and potentially ancient substructure within Native American, European, and West African source populations. Here, we quantify genome-wide patterns of SNP and haplotype variation among 100 individuals with ancestry from Ecuador, Colombia, Puerto Rico, and the Dominican Republic genotyped on the Illumina 610-Quad arrays and 112 Mexicans genotyped on Affymetrix 500K platform. Intersecting these data with previously collected high-density SNP data from 4,305 individuals, we use principal component analysis and clustering methods FRAPPE and STRUCTURE to investigate genome-wide patterns of African, European, and Native American population structure within and among Hispanic/Latino populations. Comparing autosomal, X and Y chromosome, and mtDNA variation, we find evidence of a significant sex bias in admixture proportions consistent with disproportionate contribution of European male and Native American female ancestry to present-day populations. We also find that patterns of linkage disequi-

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libria in admixed Hispanic/Latino populations are largely affected by the admixture dynamics of the populations, with faster decay of LD in populations of higher African ancestry. Finally, using the locus-specific ancestry inference method LAMP, we reconstruct fine-scale chromosomal patterns of admixture. We document moderate power to differentiate among potential subcontinental source populations within the Native American, European, and African segments of the admixed Hispanic/Latino genomes. Our results suggest future genome-wide association scans in Hispanic/Latino populations may require correction for local genomic ancestry at a subcontinental scale when associating differences in the genome with disease risk, progression, and drug efficacy, as well as for admixture mapping.

The term "Hispanic/Latinos" refers to the ethnically diverse inhabitants of Latin America and to people of Latin American descent throughout the world. Present-day Hispanic/Latino populations exhibit complex population structure, with significant genetic contributions from Native American and European populations (primarily involving local indigenous populations and migrants from the Iberian peninsula and Southern Europe) as well as West Africans brought to the Americas through the trans-Atlantic slave trade (Sans, 2000; S. Wang et al., 2008). These complex historical events have affected patterns of genetic and genomic variation within and among present-day Hispanic/Latino populations in a heterogeneous fashion, resulting in rich and varied ancestry within and among populations as well as marked differences in the contribution of European, Native American, and African ancestry to autosomal, X chromosome, and uniparentally inherited genomes.

Many key demographic variables differed among colonial Latin American populations, including the population size of the local pre-Columbian Native American population, the extent and rate at which European settlers displaced native populations, whether or not slavery was introduced in a given region, and, if so, the size and timing of introduction of the African slave populations. There were also strong differences in ancestry among social classes in colonial (and postcolonial) populations with European ancestry often correlating with higher social standing. As a consequence, present-day Hispanic/Latino populations exhibit very large variation in ancestry proportions (as estimated from genetic data) not only across geographic regions (Sans, 2000; S. Wang et al., 2008), but also within countries themselves (Seldin et al., 2007; Silva-Zolezzi et al., 2009). In addition, the process of admixture was apparently sex-biased and preferentially occurred between European males and Amerindian and/or African females; this process has been shown to be remarkably

consistent among countries and populations including Argentina (Dipierri et al., 1998), Ecuador (González-Andrade et al., 2007), Mexico (Green et al., 2000), Cuba (Mendizabal et al., 2008), Brazil (Marrero et al., 2007), Uruguay (Sans et al., 2002), Colombia (Carvajal-Carmona et al., 2003), and Costa Rica (Carvajal-Carmona et al., 2003).

The rich diversity of variation in ancestry among Hispanic/Latino populations, coupled with consistent differences among populations in the incidence of chronic heritable diseases, suggests that Hispanic/Latino populations may be very well suited for admixture mapping (Smith et al., 2001; González Burchard et al., 2005). For example, differences in relative European ancestry proportions correlate with higher susceptibility in Puerto Ricans to asthma as compared with Mexicans (Salari et al., 2005). Data have also shown an increased risk of breast cancer in Latinas with greater European ancestry (Fejerman et al., 2008) and an interplay between African ancestry and cardiovascular disease and hypertension in Puerto Ricans from Boston (Lai et al., 2009). Hispanic/Latinos are also likely to play an increasingly important role in multi- and transethnic genetic studies of complex disease. Genome-wide scans have identified candidate markers for onset of type 2 diabetes in Mexican-Americans from Texas (Hayes et al., 2007) as well as a region on chromosome 5 associated with asthma in Puerto Ricans (Choudhry et al., 2008).

Quantifying the relative contributions of ancestry, environment (including socioeconomic status), and ancestry by environment interaction to disease outcome in diverse Hispanic/Latino populations will also be critical to applying a genomic perspective to the practice of medicine in the United States and in Latin America. For example, whereas European ancestry was associated with increased asthma susceptibility in Puerto Ricans (Salari et al., 2005), it was also shown that the effect was moderated by socioeconomic status (Choudhry et al., 2006). This suggests that quantifying fine-scale patterns of genomic diversity among diverse U.S. and non-U.S. Hispanic/Latinos may be critical to the efficient and effective design of medical and population genomic studies. A fine-scale population genomics perspective may also provide a powerful means for understanding the roles of ancestry, genetics, and environmental covariates on disease onset and severity (González Burchard et al., 2005).

Here, we introduce a larger, high-density SNP and haplotype dataset to investigate historical population genetics questions—such as variation in sex-biased ancestry and genome-wide admixture proportions within and among Latino populations—as well as provide a genomic resource for the study of population substructure within putative European, African, and Native American source populations. Our dataset includes three Latino populations that are underrepresented in whole-genome analyses, namely, Dominicans, Colombians, and Ecuadorians, as well as Mexicans

and Puerto Ricans, the two largest Hispanic/Latino ethnic groups in the United States. This allows comparison of patterns of population structure and ancestry across multiple U.S. Hispanic/Latino populations. Our dense SNP marker panel is formed by the intersection of two of the most commonly used genotyping platforms, allowing for the inclusion of dozens of Native American, African, and European populations for ancestry inference. Our work expands on high-density population-wide genotype data from the International HapMap Project (HapMap) (International HapMap Consortium, 2005; Frazer et al., 2007), the Human Genome Diversity Panel (HGDP) (Rosenberg et al., 2002), and the Population Reference Sample (POPRES) (Nelson et al., 2008) that have representation of Mexicans but not other Hispanic/Latino groups either from the Caribbean or from South America, with a resulting gap for analyzing admixture in those populations. This project, therefore, represents an important step toward comprehensive panels for U.S.-based studies that can more accurately reflect the diversity within various Hispanic/Latino populations.

## RESULTS

### Population Structure

We applied the clustering algorithm *FRAPPE* to investigate genetic structure among Hispanic/Latino individuals using a merged data set with over 5,000 individuals with European, African, and Native American ancestry genotyped across 73,901 SNPs common to the Affymetrix 500K array and the Illumina 610-Quad panel (*Materials and Methods*). *FRAPPE* implements a maximum likelihood method to infer the genetic ancestry of each individual, where the individuals are assumed to have originated from $K$ ancestral clusters (Tang et al., 2005). The plots for $K = 3$ and $K = 7$ are shown in Fig. 8.1 and for all other values of $K$ in Fig. S1 (available online at www.pnas.org/cgi/content/full/0914618107/DCSupplemental) $K = 3$. We observed clustering largely by Native American, African, and European ancestry, with the Hispanic/Latino populations showing genetic similarity with all of these populations. However, significant population differences exist, with the Dominicans and Puerto Ricans showing the highest levels of African ancestry (41.8% and 23.6% African, SDs 16% and 12%), whereas Mexicans and Ecuadorians show the lowest levels of African ancestry (5.6% and 7.3% African, SDs 2% and 5%) and the highest Native American ancestries (50.1% and 38.8% Native American, SDs 13% and 10%). We also found extensive variation in European, Native American, and African ancestry among individuals within each population. A clear example could be observed in the Mexican sample, in which ancestry proportions ranged from predominantly Native American to predomi-

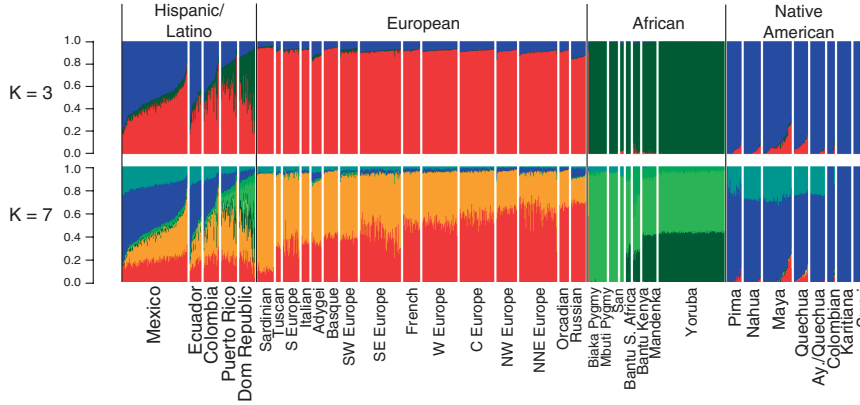


FIGURE 8.1 *FRAPPE* clustering illustrating the admixed ancestry of Hispanic/Latinos shown for $K = 3$ and $K = 7$. Individuals are shown as vertical bars shaded in proportion to their estimated ancestry within each cluster. Native American populations are listed in order geographically, from North to South.

nantly European (with generally low levels of African ancestry). Similar results were found in Colombians and Ecuadorians, whereas Dominicans and Puerto Ricans showed the greatest variation in the African ancestry (Fig. 8.1). Interestingly, at K = 7, we were able to capture signals of continental substructure such as a Southwest to Northeast gradient in Europe and a Native American component that is absent in the two Amazonian indigenous populations (Karitiana and Surui) but that substantially contributes to all other studied Latino populations. We also note that several of the individuals from the Maya and Quechua Native American samples (and to a lesser extent Nahua and Pima) from the Human Genome Diversity Panel (CEPH-HGDP) show moderate levels of European admixture, consistent with previous studies of these populations (Jakobsson et al., 2008). Interestingly, this is not the case for the Aymara and Quechua samples genotyped by Mao et al. (2007).

We also undertook principal component analysis (PCA) of the autosomal genotype data from Hispanic/Latino and putative ancestral populations using the *smartpca* program from the software package *eigenstrat* (Fig. 8.2*A*) (Patterson et al., 2006a). The first two principal components of the PCA strongly support the notion that the three ancestral populations contributing to the Hispanic/Latino genomic diversity correspond exactly to Native American, European, and African ancestry. The Hispanic/Latino populations showed different profiles of ancestry, as exemplified by the fitting of ellipses to the covariance matrix of each population's first two PCs (Fig. 8.2*C*). Subsequent PCs showed substructure within Africa, Native

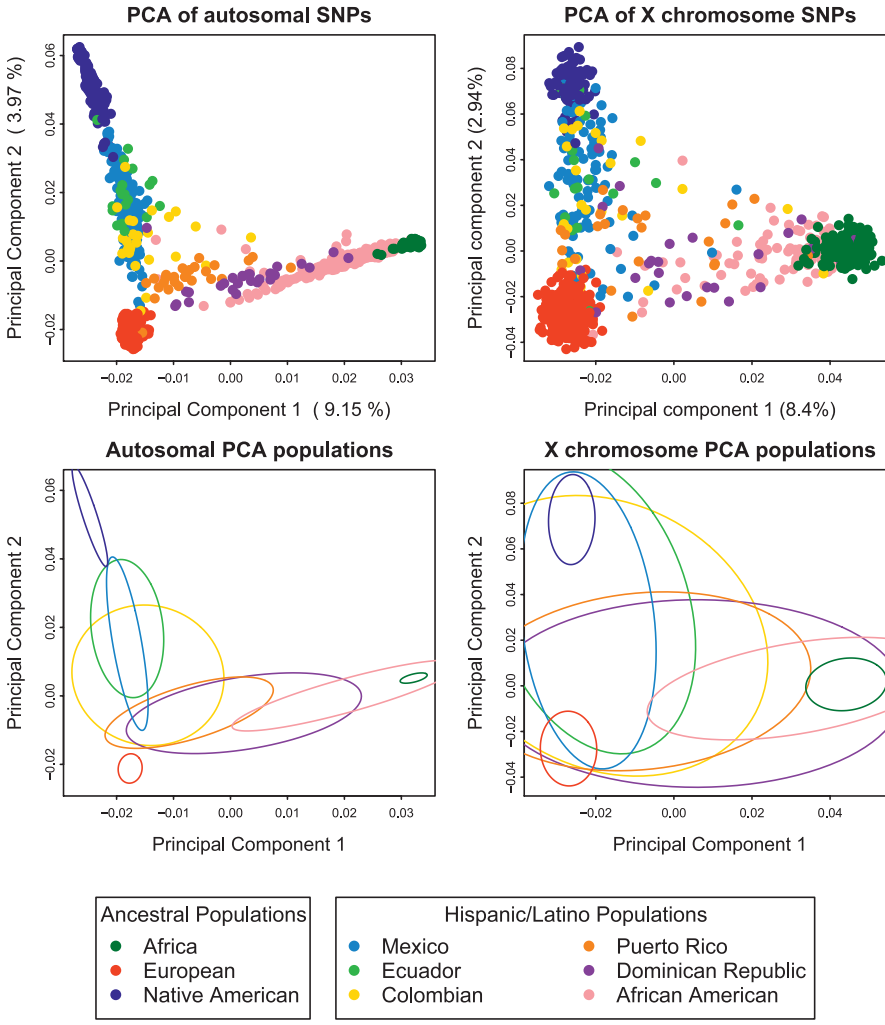


FIGURE 8.2 Principal component analysis results of the Hispanic/Latino individuals with Europeans, Africans, and Native Americans. PC1 vs. PC2 scatterplots based on autosomal markers (*Upper Left*) and based on X chromosome markers (*Upper Right*). Ellipses are fitted to the PCA results on the autosomes (*Lower Left*) and to results from the X chromosome markers (*Lower Right*).

Americans, and Europeans (Fig. S2, available online at www.pnas.org/cgi/content/full/0914618107/DCSupplemental). PCA on the X chromosome markers (Fig. 8.2*B*) showed a similar pattern, although because there are only 1,500 markers, this PCA had greater variance, which is illustrated in the fitted ellipses as well (Fig. 8.2*D*).

We also ran the Bayesian clustering algorithm *STRUCTURE* in "assignment mode" (Falush et al., 2003), and used a training set of Europeans, Africans, and Native Americans to estimate ancestral allele frequencies and assess admixture proportions within and among the Hispanic/Latino populations. Using *STRUCTURE* analysis of the autosomes (Fig. 8.3, *Upper*) and the X chromosome (Fig. 8.3, *Lower*), we found that, again, Puerto Ricans and Dominicans showed the greatest proportion of African ancestry whereas Colombians, Ecuadorians, and Mexicans showed extensive variation in European and Native American ancestry among individuals. We calculated LD decay curves for all populations with at least

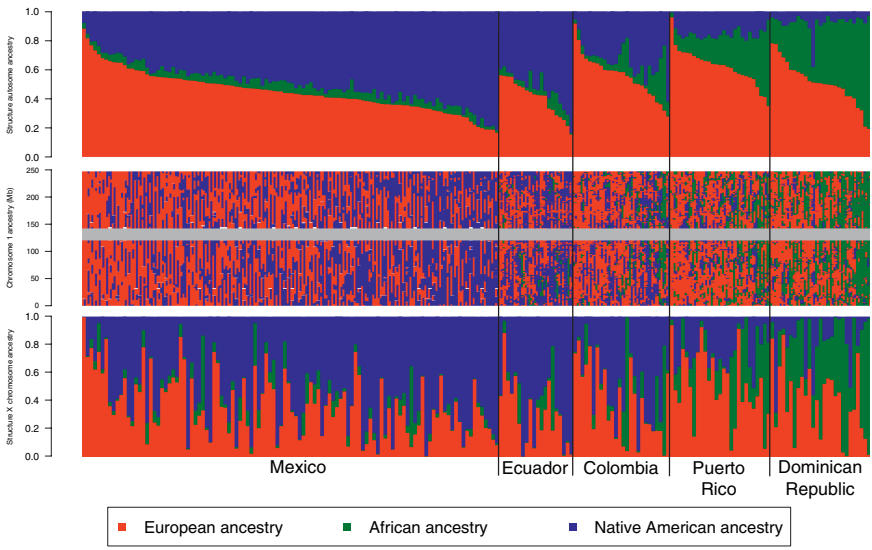


FIGURE 8.3 Genome-wide and locus-specific ancestry estimates for Mexicans, Ecuadorians, Colombians, Puerto Ricans, and Dominicans. Shown for $K = 3$, clustering of the Hispanic/Latino individuals on the autosomes (*Top*) and on the X chromosome (*Bottom*). Individuals are shown as vertical bars shaded in proportion to their estimated ancestry within each cluster. Local ancestry at each locus is shown for each individual on chromosome 1 (*Middle*). The X chromosome shows greater Native American ancestry and greater variability in African ancestry, with reduced European ancestry.

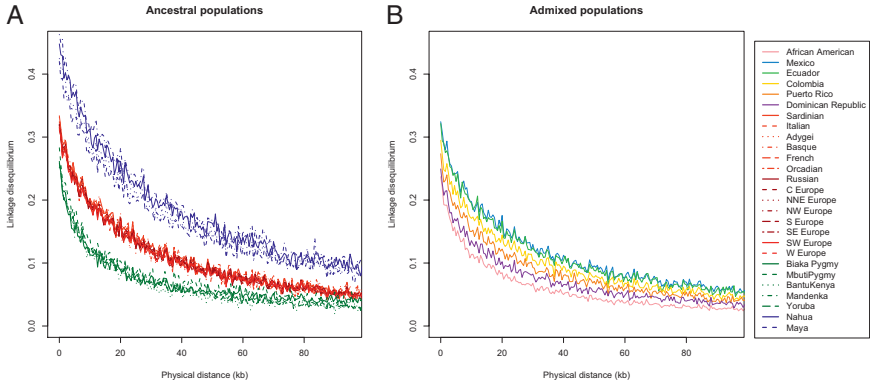


FIGURE 8.4 Linkage disequilibrium, genotype $r^2$ estimated by PLINK, by population as a function of physical distance (Mb). (*Left*) Native American, European, and African populations. (*Right*) Hispanic/Latino populations. Scale is the same.

10 individuals, choosing subsets of 10 individuals, and averaging more than 100 random subsets of the data. Patterns of decay of LD were consistent with previously published results (Jakobsson et al., 2008), with Native American populations showing the highest levels of LD and African populations the lowest (Fig. 8.4*A*). Interestingly, the Hispanic/Latino populations demonstrated rates of decay of LD that correlated strongly with the amount of Native American, European, and African ancestry (Fig. 8.4*B*). Specifically, the populations with the most Native American ancestry, Mexican and Ecuadorian, exhibited higher levels of linkage disequilibrium among SNP markers, whereas the populations with the highest proportions of African ancestry, the Dominican and Puerto Rican samples, had the lowest levels of LD.

## Locus-Specific Ancestry

To reconstruct local genomic ancestry at a fine scale, we used the ancestry deconvolution algorithm LAMP (Sankararaman et al., 2008), allowing for a three-way admixture and focused on the four Hispanic/Latino populations genotyped on the Illumina 610-Quad platform—Dominicans, Colombians, Puerto Ricans, and Ecuadorians (*Materials and Methods*). Because this same SNP panel had also been genotyped across the HGDP samples (1,043 individuals from 53 populations), the merged dataset containing more than 500,000 markers provided a unique resource for investigating the extent of subcontinental ancestry among diverse Hispanic/Latino populations. We found that individual average ances-

tries are in agreement with *FRAPPE* and *STRUCTURE* results in which Ecuadorians have the highest Native American proportions, followed by Colombians (showing greater European contribution), and with Puerto Ricans and Dominicans showing the highest African ancestry—specially Dominicans, who show very low contribution from Native Americans (Fig. 8.1). We also used the PCA-based methods of Bryc et al. (2010) to infer ancestry at each locus for the samples genotyped on the Affymetrix 500K, which included more than 100 Mexican samples genotyped by the POPRES project (Nelson et al., 2008) and diverse Native American populations genotyped by Mao et al. (2007). The local admixture tracks for each individual are in large agreement with the genome-wide average ancestry proportions (Fig. 8.3, *Middle*).

To investigate the genetic relationships among admixed Hispanic/Latino populations and putative ancestral groups, we compared patterns of population divergence among the inferred segments of European, African, and Native American ancestry and corresponding putative source populations using Wright's $F_{ST}$ measure. Specifically, we used LAMP to reconstruct for each individual in our dataset, segments of European, African, and Native American ancestry across both the maximal SNP dataset for all of the admixed and putative source population individuals (i.e., either the 610K Illumina for Puerto Rican, Ecuadorian, Columbian, and Dominican or 500k for Mexicans from Guadalajara) as well as ~70k SNPs common to both platforms. To calculate $F_{ST}$ at a given SNP for a given pair of populations, we included only individuals with unambiguous ancestry assignment (i.e., individuals with two European-, two Native American–, or two African-origin chromosomes). One potential confounder for this analysis is that sample sizes differ substantially among subpopulations within major continental regions (e.g., in the Native American set, we have sample sizes that range from $n = 7$ for Colombian indigenous Americans in HGDP to $n = 29$ for Nahua from Mexico in the Mao et al. dataset). To minimize the potential bias of differences in sample size, we randomly selected $n = 7$ individuals from all potential subpopulations and recomputed Wright's $F_{ST}$. As seen in Table 8.1, we found that consistent with historical records, our results show that African segments of the Hispanic/Latino populations are more closely related to the Bantu-speaking populations of West Africa than other populations. Specifically, we found that the Colombians and Ecuadorians are most closely related to the Kenyan Bantu populations, whereas the Puerto Ricans and Dominicans are closest to the Yoruba from Nigeria. Likewise, European segments show the lowest $F_{ST}$ values when compared with Southwest European populations (individuals from Spain and Portugal), as well as French and Italian individuals. Native American segments of the Hispanic/Latino individuals show the least genetic differentiation with Mesoamerican (e.g., Maya and Nahua),

TABLE 8.1 Ancestry-Specific $F_{ST}$ Distances Between Hispanic/Latino Populations and Different Putative Source Populations

African Segments of the Genome (%)

| | Bantu Kenya | Bantu S. Africa | Biaka Pygmy | Mandenka | Mbuti Pygmy | YRI |
|---|---|---|---|---|---|---|
| COL | 3.191 | 3.375 | 6.520 | 3.677 | 11.217 | 3.263 |
| DOM | 1.564 | 1.476 | 4.657 | 1.419 | 8.877 | 0.913 |
| ECU | 6.098 | 6.883 | 10.143 | 6.400 | 14.702 | 6.481 |
| PRI | 2.500 | 2.543 | 5.761 | 2.384 | 10.216 | 2.176 |

European Segments of the Genome (%)

| | Adygei | Basque | European ESE | Europe C | Europe NNe | Europe NW | Europe S | Europe SE |
|---|---|---|---|---|---|---|---|---|
| COL | 1.836 | 1.351 | 1.389 | 0.978 | 1.253 | 1.240 | 1.033 | 1.020 |
| DOM | 1.560 | 1.128 | 1.071 | 0.691 | 0.919 | 0.940 | 0.705 | 0.775 |
| ECU | 1.669 | 1.456 | 1.225 | 1.012 | 1.212 | 1.100 | 1.005 | 1.005 |
| PRI | 1.811 | 1.530 | 1.392 | 1.062 | 1.345 | 1.251 | 1.107 | 1.181 |
| Mexico | 1.014 | 0.784 | 0.559 | 0.335 | 0.438 | 0.442 | 0.193 | 0.307 |

Native American Segments of the Genome (%)

| | Aymara | Colombian | Karitiana | Maya | Nahua | Pima | Quechua | Surui |
|---|---|---|---|---|---|---|---|---|
| COL | 4.005 | 5.296 | 9.099 | 4.724 | 3.614 | 8.562 | 3.432 | 13.803 |
| DOM | 5.142 | 5.868 | 9.060 | 4.262 | 3.601 | 9.310 | 3.147 | 13.736 |
| ECU | 4.244 | 5.799 | 9.178 | 5.446 | 4.147 | 9.193 | 3.079 | 13.765 |
| PRI | 5.872 | 6.618 | 10.120 | 6.624 | 4.795 | 10.578 | 5.169 | 15.093 |
| Mexico | 2.397 | 4.185 | 8.197 | 1.417 | 0.572 | 5.112 | 2.086 | 11.061 |

NOTE: Results based on ~70k overlapping SNPs between Affymetrix and Illumina platforms and equalizing population sample sizes down to seven individuals per population.

| Europe SW | Europe W | French | Italian | Orcadian | Russian | Sardinian | Tuscan |
|---|---|---|---|---|---|---|---|
| 0.863 | 1.080 | 0.880 | 0.885 | 1.410 | 1.648 | 1.550 | 1.050 |
| 0.537 | 0.730 | 0.613 | 0.610 | 1.093 | 1.413 | 1.270 | 0.825 |
| 0.838 | 1.104 | 0.799 | 0.845 | 1.417 | 1.369 | 1.607 | 0.925 |
| 0.916 | 1.155 | 0.940 | 0.879 | 1.508 | 1.820 | 1.566 | 1.041 |
| 0.122 | 0.265 | 0.270 | 0.271 | 0.793 | 0.882 | 0.852 | 0.336 |

Chibchan (e.g., Colombian), and Andean (e.g., Quechua) populations. The closest relationship is clearly observed between Mexicans from Guadalajara and Nahua indigenous individuals.

### Sex Bias in Ancestry Contributions

We used the *STRUCTURE* ancestry estimates on the autosomes and X chromosome to estimate Native American, European, and African ancestry proportions of each Hispanic/Latino individual. We then compared the estimates of ancestry for each population on the autosomes vs. on the X chromosome [Fig. 8.5 and Figs. S3 and S4 (available online at www.pnas.org/cgi/content/full/0914618107/DCSupplemental)]. Whereas the Native American ancestry was significantly higher on the X chromosome than on the autosomes (including those populations with reduced Native American ancestry, i.e., Puerto Ricans and Dominicans), the autosomal vs. X-chromosome difference was more attenuated with regard to African ancestry. This reduced deviation is present even in those Hispanic/Latino populations analyzed whose non-European ancestry was principally

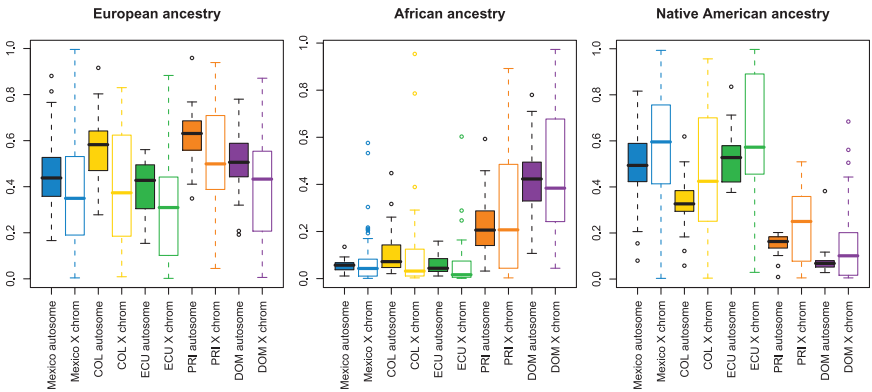


FIGURE 8.5 Boxplots comparing autosomal vs. X-chromosome ancestry proportions by population, shown for European ancestry (*Left*), Native American ancestry (*Center*), and African ancestry (*Right*). Filled boxes correspond to autosomal ancestry estimates; open boxes show X-chromosome ancestry estimates. Median (solid line), first and third quartiles (box) and the minimum/maximum values, or to the smallest value within 1.5 times the IQR from the first quartile (whiskers). For each paired comparison of X chromosomes and autosomes, median Native American ancestries are consistently higher on the X chromosome in all Hispanic/Latino populations sampled, and European ancestries are lower across all populations.

Native American in origin (i.e., Mexicans and Ecuadorians). Furthermore, greater Native American ancestry on the X chromosome in Puerto Ricans did not necessarily imply greater Amerindian ancestry on the autosomes. This finding is similar to those observed by analyzing fine-scale genome pattern of population structure and admixture among African Americans, West Africans, and Europeans (Lind et al., 2007).

Finally, we used SNP and microsatellite genotyping to identify the canonical Y chromosome and mtDNA haplotypes for each of the Hispanic/Latino individuals that we genotyped. Details of the loci and classifications are found in Tables S1 and S2 (available online at www.pnas.org/cgi/content/full/0914618107/DCSupplemental). We found an excess of European Y chromosome haplotypes and a higher proportion of Native American and African mtDNA haplotypes, consistent with previous studies (Fig. 8.6). In addition, we found several non-European Y chromosomal haplotypes with most likely origins from North Africa and the Middle East. We observed that African-derived haplotypes were the predominant origin of mtDNA in Dominicans (17 of 27 individuals), matching the greater African vs. Native American origins of this population on the autosomes and X chromosomes. However, in Puerto Ricans we did not find evidence of a high African female contribution. The predominant Y chromosomal origins in the Puerto Ricans sampled were European and

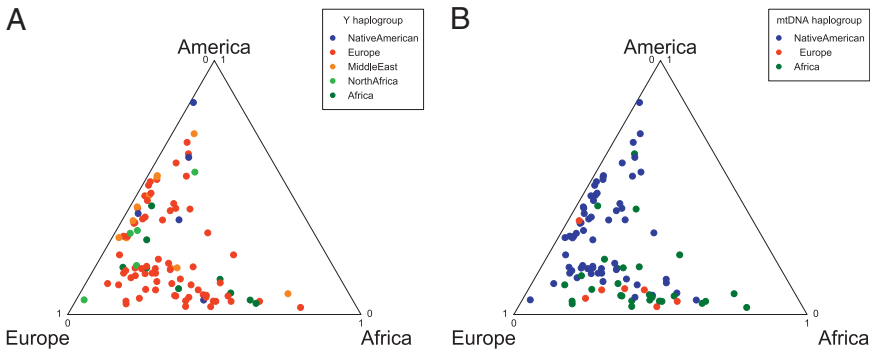


FIGURE 8.6 Comparison of mtDNA and Y chromosome haplotypes. Each individual is represented by a point within the triangle that represents the autosomal ancestry proportions. The most probable continental location for each individual's haplotype is designated by the shade of the point. The Y chromosome contains a disproportionate number of European haplotypes, whereas the mtDNA has a high proportion of Native American, slightly more African haplotypes, and fewer European haplotypes, consistent with a sex bias toward a great European male and Native American/African female ancestry in the Hispanic/Latinos.

African; but, in contrast, 20 of 27 Puerto Rican individuals had mitochondrial haplotypes of Native American origin, suggesting a strong female Native American and male European and African sex bias contribution. Overall, in all of the Hispanic/Latino populations that we analyzed, we found evidence of greater European ancestry on the Y chromosome and higher Native American ancestry on the mtDNA and X chromosome consistent with previous findings (Dipierri et al., 1998; Green et al., 2000; Sans et al., 2002; Carvajal-Carmona et al., 2003; González-Andrade et al., 2007; Marrero et al., 2007; Mendizabal et al., 2008).

## DISCUSSION

Our work has important implications for understanding the population genetic history of Latin America as well as ancestry of U.S.-based Hispanic/Latino populations. As has been previously documented, we found large variation in the proportions of European, African, and Native American ancestry among Mexicans, Puerto Ricans, Dominicans, Ecuadorians, and Colombians, but also within each of these groups. These trends are a consequence of variation in rates of migration from ancestral European and African source populations as well as population density Native Americans in pre-Columbian times (Sans, 2000). We found that Dominicans and Puerto Ricans in our study showed the highest levels of African ancestry, consistent with historical records. European settlers to island nations in the Caribbean basin largely displaced Native American populations by the early to mid-16th century and concurrently imported large African slave populations for large-scale colonial agricultural production (largely of sugar). In contrast, Colombia has wider geographic differences ranging from Caribbean coasts to Andean valleys and mountains, which could explain the enrichment of African ancestry in some individuals and not in others, likely representing the differences in origin within Colombia. Finally, Mexico and Ecuador are two continental countries that had high densities of Native Americans during pre-Columbian times; as expected, the individuals from these two countries show the highest degree of Native American ancestry. Our findings clearly show that the involuntary migration of Africans through the slave trade appears to have left a clear trace in Hispanic/Latino populations proximal to these routes.

From the $F_{ST}$ analysis, we found that the high-density genotype data that we have collected is quite informative regarding the personal genetic ancestry of admixed Hispanic/Latino individuals. Specifically, we found that individuals differ dramatically within and among populations and that we can reliably identify subpopulations within major geographic regions (i.e., Europe, Africa, and the Americas) that exhibit lower pairwise

$F_{ST}$ (and, therefore, higher genetic similarity) to the inferred European, African, and Native American segments for the 212 individuals studied. We found, for example, that Nahua showed the lowest $F_{ST}$ in Mexicans, consistent with the observation that the Nahua are one of the largest Native American populations in this region and are likely to have contributed to the genomes of admixed individuals in Mexico (as opposed, for instance, to the Mexican Pima who fall outside the Mesoamerican cultural region and show considerably higher levels of differentiation). We also found that the lowest $F_{ST}$ for the African regions of the Dominican and Puerto Rican genomes are with the Yoruba, a Bantu-speaking West African population that has been shown to be genetically similar to the African segments of African Americans sampled in the United States (Bryc et al., 2010). Although we have limited Native American populations and Hispanic/Latino sample sizes and, thus, the differences in $F_{ST}$ with different subcontinental populations suggest that there exists a reasonably strong signal of which present-day populations are most closely related to the ancestral populations that contributed ancestry to each of the Hispanic/Latino populations.

When comparing inferred continental ancestry of the X and Y chromosomes and mitochondrial vs. the autosomal genome, we observed an enrichment of European Y-chromosome vs. autosomal genetic material, and a greater percentage of both Native American and African ancestry on the X-chromosomes and mtDNA compared with the autosomes for the Hispanic/Latino individuals in this study. This suggests a predominance of European males and Native American/African females in the ancestral genetic pool of Latinos, consistent with previous studies. A particularly interesting observation from our work on sex-biased admixture is that the pattern exists not only within populations but among Hispanic/Latino populations as well. In all populations studied, there is an enrichment of Native American ancestry both on the X chromosome and mtDNA compared with the autosomes. This would suggest a greater female Native American contribution to the genome of Latinos. A different result was obtained in relation to African ancestry. We found a smaller difference between mean African ancestry on the X chromosome and the autosomes, compared with the difference in Native American ancestry. Furthermore, unlike in Native American ancestry, we found an overwhelming representation of Native American mtDNA haplogroups in Puerto Ricans, even though non-European ancestry on the autosomes was largely African.

It is important to note that this observation does not necessarily undermine the model of sex-biased admixture among European male and African females in the founding of Hispanic/Latino populations, especially when one considers the predominance of European Y chromosomes in all groups studied. However, it suggests that admixture between Euro-

pean males and Amerindian/African females has been a complex process in the formation of the various Hispanic/Latino populations. Specifically, a reduced X vs. autosome mean African ancestry compared with Native American ancestry suggests a more balanced gender contribution in the Hispanic/Latino genome by individuals of African ancestry. In the case of Puerto Ricans, the only way that one can reconcile greater African ancestry on the X chromosome vs. what would be expected on mitochondrial data would be through transmission of X chromosomes independent of mitochondrial transmission, which is plausible biologically only via males. Caution, however, should be exercised before considering such conclusions as concrete; unlike X chromosomes, which can recombine and thus represent haplotypes derived from thousands of individuals, mitochondrial DNA represents just a sole distant ancestor among these thousands. Thus, a larger mtDNA sample would be necessary compared with X chromosomes to have similar confidence that a cohort would accurately reflect the presumed diversity of ancestry in the population as a whole.

The Y chromosomal results also demonstrate the insufficiency of the paradigm of European males and Native American/African females to capture the complexity within the Latin American populations. For example, we find Y chromosomal haplotypes in Hispanic/Latinos with presumed origins in the Middle East and Northern Africa. Given that historical documentation suggests that most of the non-African and non–Native American contribution to admixed Hispanic/Latino populations is from Southwest Europe, this suggests that the contemporary populations inherited these Y chromosomes from Europeans who, in turn, were descended from Middle Eastern or North African men. Several historical events could have led to the acquisition by Europeans of non-European haplotypes, perhaps during the period of the Roman Empire when the Mediterranean Sea behaved as a conduit (not a physical barrier) between Europe, the Middle East, and North Africa or by Sephardic Jews or Moorish Muslims during the European Middle Ages/Islamic Golden Age. Alternatively, the presence of non-European Y chromosomal haplotypes originating from the Middle East and North Africa could represent the result of Iberian Jews and Muslims (themselves admixed) fleeing the peninsula for New World territories in response to discriminatory policies that strongly pressured both communities at the termination of the Reconquista. Essentially, the diversity of haplotypes in the Y chromosomes in Latinos reflects not only population dynamics from the 15th century onward, but also the historical trends of population movement occurring across the Atlantic during centuries prior.

The marked genetic heterogeneity of Latino populations shown in this study, as previously suggested by other surveys of genetic ancestry (Mao et al., 2007; Price et al., 2007; S. Wang et al., 2008) has important

implications for the identification of disease-associated variants that differ markedly in frequency among parental populations. In their study of 13 Mestizo populations from Latin America, for example, S. Wang et al. (2008) suggested that admixture mapping in Hispanic/Latino populations may be feasible within a two-population admixture framework, since the mean African ancestry in Mestizo populations is typically low (<10%) (S. Wang et al., 2008). Although this is true for Hispanic/Latino populations with origins in the continental landmass of the Americas (such as the populations studied by S. Wang et al.), our results show that this may not apply to Latino populations with origins in the Caribbean, as their African ancestry proportion is considerably higher and is highly variable among individuals, suggesting an extensive three-way admixture and representing additional challenges for admixture mapping. Likewise, we find subtle but reproducible differences in subcontinental ancestry among Hispanic/Latino individuals, suggesting that even a three-way admixture model may not be sufficient to accurately model the dynamic population genetic history of these populations.

Another observation with important implications for designing association studies is the large variation in individual admixture estimates within certain Latino populations (e.g., Mexicans, Colombians, and Ecuadorians). One could expect such outcome when collecting samples from U.S.-based Latino communities, which in turn may come from different locations within their countries of origin (e.g., Colombians and Ecuadorians). However, within the Mexican sample, which has been collected in a single sampling location (i.e., Guadalajara, Mexico), we also observed large variation in European vs. Native American admixture proportions. Our findings are in agreement with previous studies on genetic ancestry from Mexico City (Martinez-Marignac et al., 2007; S. Wang et al., 2008), supporting the idea that such urban agglomerations, in which a large number of epidemiological studies are likely to take place, continue to host a wide range of genetic variability among individuals that may self-identify as individuals from the same population. Therefore, particular attention should be paid to carefully matching representative cases and controls, as well as to carefully control for ancestry when performing association studies using Hispanic/Latino populations. We hope that our dense genome-wide admixture analysis has allowed greater insight into the population dynamics of multiple Hispanic/Latino populations and that it will provide a resource for designing next-generation epidemiological studies in these communities, opening the possibility of better understanding the genetic makeup of this growing segment of the U.S. population.

## MATERIALS AND METHODS

### Datasets

We genotyped 100 individuals with ancestry from Puerto Rico, the Dominican Republic, Ecuador, and Colombia on Illumina 610K arrays. We extracted 400 European, 365 African American, and 112 Mexican samples from the GlaxoSmithKline POPRES project, which is a resource of nearly 6,000 control individuals from North America, Europe, and Asia genotyped on the Affymetrix GeneChip 500K Array Set (Nelson et al., 2008). We randomly sampled 15 individuals from each European country where possible, or the maximum number of individuals available otherwise, to select the POPRES European individuals to be included in our study. Further description of sampling locations, genotyping, and data quality control are available elsewhere (Nelson et al., 2008). We include 165 and 167 individuals from the HapMap project from the CEU and YRI populations, thinned to the same SNP set (Frazer et al., 2007). We also include all European, Native American, and African individuals from the HGDP genotyped on Illumina 610K arrays (Jakobsson et al., 2008). Finally, we include all Native American populations from the Mao et al. (2007) study genotyped on Affymetrix 500K arrays. For each dataset, we used annotation information to determine the strand on which the data were given and to map all Affymetrix and Illumina marker ids to corresponding dbSNP reference ids [rsids]. SNPs without valid rsids were excluded from analysis. Each dataset was then converted to the forward strand to facilitate merging of the data. Data from the various platforms were merged using the PLINK toolset, version 1.06 (Purcell et al., 2007). Likewise, nonmissing genotype calls that showed disagreement between datasets were omitted. Demographic data for all individuals included in this study are available on GenBank. All samples were approved by institutional review board protocols from their respective studies.

### Data Quality Control

The HapMap II release 23, HGDP, Mao et al., and POPRES samples were genotyped and called according to their respective quality control procedures (Frazer et al., 2007; Mao et al., 2007; Jakobsson et al., 2008; Nelson et al., 2008). Our final merged dataset contains 73,901 SNPs with genotype missingness of $<0.1$ and $<0.05$ individual missingness across 5,104 individuals.

**Population Structure**

We used the software *FRAPPE*, which implements an expectation-maximization algorithm for estimating individual membership in clusters (Tang et al., 2005). This algorithm is more computationally efficient than other MCMC methods, allowing it to analyze many more markers than, for example, *STRUCTURE* (Falush et al., 2003; Tang et al., 2005). After thinning markers to have $r^2 < 0.5$ in 50 SNP windows, shifting and recalculating every 5 SNPs, we ran *FRAPPE* on all 64,935 remaining markers for 5,000 iterations. We also assessed admixture proportions for the Hispanic/Latino individuals using *STRUCTURE* on a reduced dataset of 5,440 markers after thinning for MAF > 0.2 and with a minimum separation of 400 kb between markers. We used the F model with USEPOPINFO = 1 to update allele frequencies using only the ancestral individuals, with 5,000 burn-in and 5,000 iterations (Falush et al., 2003). We also used all 1,518 SNPs on the X chromosome for the same analysis of the X chromosome ancestry. Principal component analysis was conducted using a dataset thinned to have $r^2 < 0.8$ in 50 SNP windows, leaving 69,212 SNPs for analysis using the package *smartpca* from the software *eigenstrat*. Ellipses were fitted following the means and 1 SD of the variance–covariance matrix of the PC1 and PC2 scores of each population.

For local ancestry estimation, we used the software LAMP in LAMPANC mode providing allele frequencies for the HGDP West Africans, Europeans, and Native Americans as ancestral populations (Sankararaman et al., 2008). A total of 552,025 SNPs were included in the analysis, and configuration parameters were set as follows: mixture proportions (alpha) = 0.2, 0.4, 0.4; number of generations since admixture ($g$) = 20; recombination rate ($r$) = 1e−8; fraction of overlap between adjacent windows (offset) = 0.2; and $r^2$ threshold (ldcutoff) = 0.1. Local ancestry estimation for the Mexican individuals was performed using the two-way PCA-based method described in Bryc et al. (2010) for both the full Illumina 610K and the Affymetrix 500K datasets, in 10 SNP windows. Only Native Americans with <0.01 European ancestry (as estimated from *FRAPPE* results) were used as the ancestral Native American individuals within their respective datasets. $F_{ST}$ was calculated between Native American, European, and African regions of the Hispanic/Latino individuals and the respective continental populations using a C++ implementation of Weir and Cockerham's (1984) $F_{ST}$ weighed equations as previously published. To eliminate bias in estimation of $F_{ST}$ due to European ancestry shown in some of the Native Americans, we also removed regions showing European ancestry within any of the Native Americans showing >0.01 European ancestry, using the same local ancestry estimation procedure as described for the Mexican individuals. Furthermore, to avoid any potentially confounding effect of sample size, we used a random sample of 7 (the minimum sample size of

the Native American populations) individuals per non-Hispanic/Latino population to calculate pairwise $F_{ST}$. MAF was set at a threshold >0.1 in the populations compared by $F_{ST}$ calculations.

## ACKNOWLEDGMENTS

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# 9

# Human Skin Pigmentation as an Adaptation to UV Radiation

NINA G. JABLONSKI*† AND GEORGE CHAPLIN*

Human skin pigmentation is the product of two clines produced by natural selection to adjust levels of constitutive pigmentation to levels of UV radiation (UVR). One cline was generated by high UVR near the equator and led to the evolution of dark, photoprotective, eumelanin-rich pigmentation. The other was produced by the requirement for UVB photons to sustain cutaneous photosynthesis of vitamin $D_3$ in low-UVB environments, and resulted in the evolution of depigmented skin. As hominins dispersed outside of the tropics, they experienced different intensities and seasonal mixtures of UVA and UVB. Extreme UVA throughout the year and two equinoctial peaks of UVB prevail within the tropics. Under these conditions, the primary selective pressure was to protect folate by maintaining dark pigmentation. Photolysis of folate and its main serum form of 5-methylhydrofolate is caused by UVR and by reactive oxygen species generated by UVA. Competition for folate between the needs for cell division, DNA repair, and melanogenesis is severe under stressful, high-UVR conditions and is exacerbated by dietary insufficiency. Outside of tropical latitudes, UVB levels are generally low and peak only once during the year. The populations exhibiting maximally depigmented skin are those inhabiting environments with the lowest annual and summer peak levels of UVB. Development of facultative pigmentation (tanning) was important to populations settling between roughly 23° and 46°, where levels of UVB varied strongly according to season. Depigmented

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and tannable skin evolved numerous times in hominin evolution via independent genetic pathways under positive selection.

Variation in skin color is the most noticeable of human polymorphisms. As visually dominant mammals, we readily notice differences in skin color in each other. As primates who uniquely use language to create categories, we readily give names to these differences. Since the mid-18th century, skin color has been the single most important physical trait used to define human groups, including variously named varieties, races, subspecies, and species. Charles Darwin observed variation in human skin color while abroad during the voyage of the *H.M.S. Beagle* (1831–1836), but he soundly rejected the notion that physical differences such as skin color constituted the basis for distinguishing separate human species (Darwin, 1871a). Darwin's rejection of the existence of distinct human species was based upon his observation that human groups "graduate into each other, and that it is hardly possible to discover clear distinctive character between them" (1871a, p. 226). His aversion to the separation of humans into discrete species was also motivated by his vehement aversion to slavery, which in his lifetime was defended and promoted on the basis of the superiority and inferiority of allegedly distinct human species (Desmond and Moore, 2009). It is also well known that early in his career, Darwin collected copious notes on human origins and descent (van Wyhe, 2007), but "without any intention of publishing on the subject, but rather with a determination not to publish, as I thought that I should thus only add to the prejudices against my views" (Darwin, 1871a, p. 1). Darwin thus deflected potential criticism of natural selection in the first decade after publication of *The Origin* by avoiding almost entirely discussion of humans in an evolutionary context.

The causes of variation in human skin pigmentation were much discussed long before Darwin's time. Observers beginning with Hippocrates in the fifth century associated human traits and temperament with the environment and recognized that skin color was part of this package (Isaac, 2004). The association of dark skin pigmentation with intense sunshine and heat was further developed by Aristotle and his followers as part of a comprehensive "climatic theory," which related human features, dispositions, and cultures to the environment. By the mid-18th century, naturalists such as John Mitchell and, later, Samuel Stanhope Smith recognized a pronounced latitudinal gradient of skin pigmentation among the world's peoples—from dark near the equator to light toward the poles—and related it mainly to differences in sunshine heat experienced by people at different latitudes (Mitchell and Collinson, 1744; Smith and

Jordan, 1965). "This general uniformity in the effect," Smith wrote, "indicates an influence in climate, that, under the same circumstances, will always operate in the same manner" (Smith and Jordan, 1965, p. 34). It is thus surprising that Darwin, who was so keen to identify adaptations of organisms to "different conditions of life," rejected a causal association of skin pigmentation with climate in favor of the notion that variations in skin color had evolved primarily through the agency of sexual selection (Darwin, 1871a). Writing in 1871 in *The Descent of Man, and Selection in Relation to Sex* (Darwin, 1871a), he stated: "If, however, we look to the races of man, as distributed over the world, we must infer that their characteristic differences cannot be accounted for by the direct action of different conditions of life, even after exposure to them for an enormous period of time" (p. 246). "It can further be shewn that the differences between the races of man, as in colour, hairyness, form of features, &c., are of the nature which it might have been expected would have been acted on by sexual selection" (p. 250).

Darwin's preference for sexual selection in matters of human variation blinded him to the importance of natural selection in producing the attributes of human skin.[1] Human skin is functionally naked and as such served for hundreds of thousands of years as the sole interface between our bodies and the environment. Lacking the covering of dense body hair that protects other mammals and exposed to the myriad physical, chemical, and biological challenges of the environment, human skin evolved under intense pressures of natural selection. The hairless condition itself did not evolve because of a partiality for smooth skin, as averred by Darwin, but primarily because of the need to lose body heat from the skin's surface during exertion and under hot environmental conditions (Zihlman and Cohn, 1988; Jablonski and Chaplin, 2000). Cooling by evaporation of eccrine sweat is impeded by thick body hair (Folk and Semken, 1991); the primary selective pressure promoting the evolution of hair loss in humans was thermoregulation. The loss of body hair in humans was accompanied by enhanced barrier functions of the stratum corneum (Montagna, 1981; Elias, 2005), including the evolution of other epidermal keratins (Chimpanzee Sequencing and Analysis Consortium, 2005; Moll et al., 2008), which reduced the skin's permeability and improved

[1]Darwin's development of sexual selection as the primary mechanism for producing visible human variation is curious and inconsistent with his views on the production of variation in other organisms. His unwillingness to implicate natural selection in connection with human variation suggests that he wanted to continue to deflect criticism of natural selection by avoiding discussion of humans being acted upon by this agency, or because he wanted to encourage discourse on human variation as being due to human *preferences* rather than being shaped by inanimate forces of nature. It is possible that he was motivated by both of these reasons.

its abilities to resist abrasion and microbial attack. The rapid divergence of genes responsible for epidermal differentiation was one of the most significant results to emerge from the initial comparison of human and chimpanzee genomes (Chimpanzee Sequencing and Analysis Consortium, 2005). Changes in skin pigmentation also accompanied loss of body hair, and multiple lines of evidence indicate that permanent, dark, eumelanin-based pigmentation evolved soon after the emergence of the genus *Homo* in Africa (Jablonski and Chaplin, 2000; Rogers et al., 2004). Sexual selection was not the primary, or even a major, determinant of skin pigmentation, although the preference by males in some cultures for females of lighter color probably has heightened sexual dimorphism in skin pigmentation in some populations (Jablonski and Chaplin, 2000). Rather, it was natural selection that produced the conspicuous gradient of skin tone groups observed in our species.

Samuel Stanhope Smith's observation of a correlation between latitude, solar processes, and human skin pigmentation was refined in the latter part of the 20th century when it was demonstrated that human skin reflectance (as a measure of skin pigmentation) was more highly correlated with latitude as a surrogate for UVR than with temperature, humidity, or altitude (Walter, 1971; Roberts and Kahlon, 1976). The introduction of geographic information systems (GIS) technology and the availability of remotely sensed environmental data permitted accurate and precise testing of the strength of the relationship between physical parameters of the environment and skin pigmentation, and demonstrated conclusively the high correlation between skin pigmentation and UVR (Jablonski and Chaplin, 2000; Chaplin, 2004). Among the most notable findings from these studies was the demonstration that skin reflectance was more highly correlated with autumn levels of UVR than with annual average, summer, or maximum levels (Chaplin, 2004). Establishment of UVR as the cause, not simply the correlate, of variations in human skin pigmentation has involved elucidation of the probable selective mechanisms involved.

During most of 20th century, arguments about the selective value of dark pigmentation focused on the protective effects of melanin against sunburn, skin cancer, and overproduction of vitamin D (Blum, 1961; Loomis, 1967). These factors can no longer be considered significant selective pressures. Sunburn and skin cancer have negligible effects on reproductive success (Blum, 1961; Jablonski and Chaplin, 2000). Nonmelanoma skin cancers are common in older individuals from modern lightly pigmented populations inhabiting sunny climes, but they are rarely fatal or incapacitating (Ricotti et al., 2009). Melanoma afflicts younger individuals and is often fatal, but it is much rarer than nonmelanoma skin cancers. Modern statistics on skin cancer prevalence must be viewed with caution, however, in considering the evolutionary importance of skin cancers. The

prevalence of skin cancers is highest in lightly pigmented people who experience chronic or intense episodic exposures to strong UVR in places far from their ancestral homelands (MacKie et al., 2009). Skin cancers are mostly a consequence of modern human migrations and resulting mismatches between skin pigmentation and geography or lifestyle. The effects of skin cancers on reproductive success in humans today are modest, and were probably statistically inconsequential in the centuries before rapid, long-distance travel and migration. This inference is further supported by genetic evidence indicating no significant association of 15 SNPs and skin cancer risk (Nan et al., 2009). Overproduction of vitamin D was refuted as the primary cause of the evolution of dark pigmentation by the discovery that hypervitamosis D due to sun exposure is physiologically impossible because of photochemical regulation (Holick et al., 1981). With the traditional agents of skin pigmentation evolution rendered untenable, we undertook a reexamination of possible selective agents.

The possibility that photolysis of folate by sunlight was a determining factor in the evolution of dark pigmentation was first explored (Branda and Eaton, 1978) before the full importance of folate in DNA biosynthesis, repair, DNA methylation, amino acid metabolism, and melanin production was recognized. In 2000, we advanced the theory that dark skin pigmentation in humans had evolved primarily to prevent reduction of fertility due to the photolysis of folate present in cutaneous blood vessels (Jablonski and Chaplin, 2000). We presented evidence that folate depletion by UVR would precipitate folate deficiencies that would, in turn, lead to potentially fatal birth defects such as neural tube defects (NTDs). Since then, investigations of the photosensitivity of folate under different conditions in vitro and in vivo have demonstrated that the relationship between skin pigmentation and folate metabolism is complicated, and involves direct photodegradation of folate (in its main form of 5-methyltetrahydrofolate or 5-MTHF) as well as its photodegradation in the presence of flavins and porphyrins by reactive oxygen species (ROS) (Off et al., 2005; Steindal et al., 2006, 2008; Tam et al., 2009). Considerable epidemiological work is needed to investigate the relationship between skin pigmentation, folate metabolism, and the prevalence of NTDs, but a protective effect of dark pigmentation against folate depletion (Lawrence, 1983; Lamparelli et al., 1988) and NTDs (Leck, 1984; Buccimazza et al., 1994) is apparent. Folate is important especially in rapidly dividing cells, such as those of the embryo and seminiferous tubules. Thus folate deficiencies caused by UVR would potentially affect both female and male fertility. Low folate levels cause derangements of folate-mediated 1-carbon metabolism that lead to serious diseases and birth defects. Folate deficiencies cause faulty DNA replication due to strand breaks caused by misincorporation of excessive uracil into DNA (Han et al., 2007; Stover, 2009). Maintenance of

adequate folate levels is associated with a 72% reduction in NTDs, which is the most common class of human birth defects (Group MVSR and MRC Vitamin Study Research Group, 1991). This is due to the direct action of folate on the normalization of neural tube development due to its role in the division of rapidly dividing cells (Fleming and Copp, 1998; Blom et al., 2006). Folate deficiency also impairs nucleotide excision repair, which is the primary mechanism for removing UVR-induced DNA photoproducts (Han et al., 2007).

Competition for folate can be severe, especially when the body is stressed by UVR exposure and insufficient dietary folate. Recent research has demonstrated that folate regulates melanin production because it is required for the synthesis of GTP, which is a substrate for de novo production of tetrahydrobiopterin (BH4) and 6BH4 in melanocytes and keratinocytes (Shi et al., 2004; Schallreuter et al., 2008). The 6BH4 in turn regulates tyrosinase activity in the melanosome (Schallreuter, 2007). Because of the manifold importance of folate and its derivatives in cell division, DNA repair, and melanin production, and because of the sensitivity of these compounds to breakdown by UVR and ROS, natural selection to protect folate levels has been intense. Maintaining the integrity of folate metabolism has a high evolutionary valence because it directly affects reproductive success and survival early in life. The mechanisms operating to prioritize the utilization of folate under conditions of environmental and cellular stress caused by high UVR levels are not yet known.

The near absence in African populations of functionally significant variation in the coding region of the melanocortin 1 receptor (*MC1R*), one of the major genes regulating human eumelanin production, indicates the action of purifying selection maintaining dark pigmentation under intense selective pressure (Harding et al., 2000; John et al., 2003; Makova and Norton, 2005). The evidence of functional constraint on *MC1R* in African populations is unusual in light of the high levels of polymorphism observed at other loci in African populations (Makova and Norton, 2005). Evidence is mounting that darkly pigmented skin, or the potential for facultative development of dark pigmentation through tanning, evolved secondarily under positive selection in populations moving from low- to high-UVR environments. Pigmentary changes such as these appear to have occurred following the dispersal of lightly and moderately pigmented "Ancestral North Indians" into high-UVR reaches of the Indian subcontinent (Reich et al., 2009) and in lightly and moderately pigmented east Asians moving into the high-UVR environments of Central and mountainous South America (Bonilla et al., 2005). Further study of the genomic signatures of selection on pigmentation genes in human population is much needed.

The evolution of light pigmentation at high latitudes has long been related to the significance of production of vitamin D in the skin under

conditions of reduced sunlight (Murray, 1934; Loomis, 1967). Vitamin $D_3$ is made in the skin when UVR penetrates the skin and is absorbed by 7-dehydrocholesterol (7-DHC) in the epidermis and dermis to form previtamin $D_3$. This reaction only occurs in the presence of wavelengths of 290–310 nm in the UVB range, with peak conversion occurring at 295–297 nm. Photosynthesis of vitamin $D_3$ in the skin depends upon the solar zenith angle, which changes with season, latitude, and time of day, and is further controlled by the amount of pigment and thickness of the skin (Mawer and Davies, 2001; Lips, 2006). The importance of vitamin $D_3$ as a selective force in the evolution of skin pigmentation is related to the manifold effects of the vitamin on fitness as reviewed in earlier papers (Jablonski and Chaplin, 2000; Chaplin and Jablonski, 2009). The vitamin D endocrine system is involved in the regulation of many independent biological processes including bone metabolism, the innate immune response, cell proliferation, and differentiation (Norman, 2008; Köstner et al., 2009). The roles of vitamin $D_3$ in the regulation of intestinal calcium absorption, and in bone formation and remodeling, have been known for decades, but only recently has the importance of vitamin $D_3$ in the establishment and maintenance of innate immunity, and in the normal functioning of the pancreas, brain, and heart, been recognized (Holick, 2004; Norman, 2008). Reduction of fertility due to vitamin $D_3$ deficiencies is greatest in cases of nutritional rickets, but is also significant because of increased prevalence of bacterial and viral infections and increased risk of autoimmune diseases such as multiple sclerosis and type 1 diabetes (Yuen and Jablonski, 2010). Natural selection to promote continued vitamin D production through loss of constitutive pigmentation under conditions of reduced UVR was strong, and its independent action on hominin populations dispersing to low-UVR habitats was inferred before genetic evidence demonstrating positive selection for depigmentation became known (Jablonski and Chaplin, 2000). Generally low and highly seasonally variable levels for UVB created a selective environment favoring the capture of UVB photons required for vitamin $D_3$ photosynthesis through loss of melanin pigmentation. Genetic verification of three independent occurrences of evolution of depigmented skin in hominin populations has been documented in the lineages leading to modern northern Europeans and modern east Asians (Lamason et al., 2005; Norton et al., 2007) and in *Homo neanderthalensis* (Lalueza-Fox et al., 2007). It is significant that the genetic and physiological mechanisms causing light-skinned phenotypes in each group were different from one another. Regulatory mechanisms involve the control of the formation of melanosomes (the organelles in which melanins are produced and stored) (Lamason et al., 2005; Norton et al., 2007), and the production of the different types and mixtures of melanins. The mechanisms whereby similar phenotypic ends have been reached by different

genetic means have been reviewed recently (Sturm, 2009). One of the most interesting questions remaining to be answered about the physiology of vitamin D in humans concerns the nature of variation in the vitamin D receptor (VDR), specifically whether the pattern and nature of polymorphisms in the VDR is related to UVB levels and/or length of habitation under specific UVB regimes.

## GEOGRAPHIC VARIATION IN UV RADIATION

Mounting genetic evidence demonstrating the role of natural selection in establishing and maintaining darkly and lightly pigmented cutaneous phenotypes near the equator and poles, respectively, prompts a closer look at the nature of the prime selective agent, UVR. Differences in the strength, seasonal distribution, and bioactivity of UVA and UVB have been recognized for a long time (Caldwell et al., 1998; Madronich et al., 1998), but the relevance of these variables to the evolution of human skin pigmentation has not been fully appreciated. The dispersals of hominins out of Africa that occurred about 1.9 Ma and 80 ka, respectively, involved the movement of people out of highly UVR-rich environments into habitats that were much more mixed with respect to the seasonal pattern, intensity, and wavelength mixture of UVR. Although two distinct forms of hominin (early *Homo* and *Homo sapiens*, respectively) were involved in these dispersals, neither form made or used clothing or used other portable methods of sun protection. Thus, apart from the time they spent in the shade, their bodies were subjected to the full force of UVR wherever they went.

The Earth's surface receives much less UVB than UVA because most UVB reaching the Earth is scattered and absorbed by oxygen, ozone, and water molecules in the atmosphere. Because of this and the geometry of sunlight reaching different places in different seasons, UVB is much more variable in its intensity and distribution than UVA. Levels of UVB are highest near the equator in more arid regions, and in high-altitude areas such as the Tibetan Plateau and the Altiplano (Fig. 9.1*A*). North or south of about 46°, levels of UVB are insufficient to initiate cutaneous production of previtamin $D_3$ for much of the year (Jablonski and Chaplin, 2000; Chaplin, 2004). The pattern of distribution of UVB is most strongly influenced by latitude because of atmospheric scattering and absorption. Africa receives high and uniform amounts, whereas northern Eurasia receives negligible amounts. The coefficient of variation (CoV) for UVB (Fig. 9.1*B*) is strongly associated with its seasonal nature outside of the tropics, and is lowest in the equatorial zone and highest in northern Eurasia and North America. Humidity and monsoon precipitation reduce average UVB, and the CoV is higher relative to the mean level in moisture-rich regions.

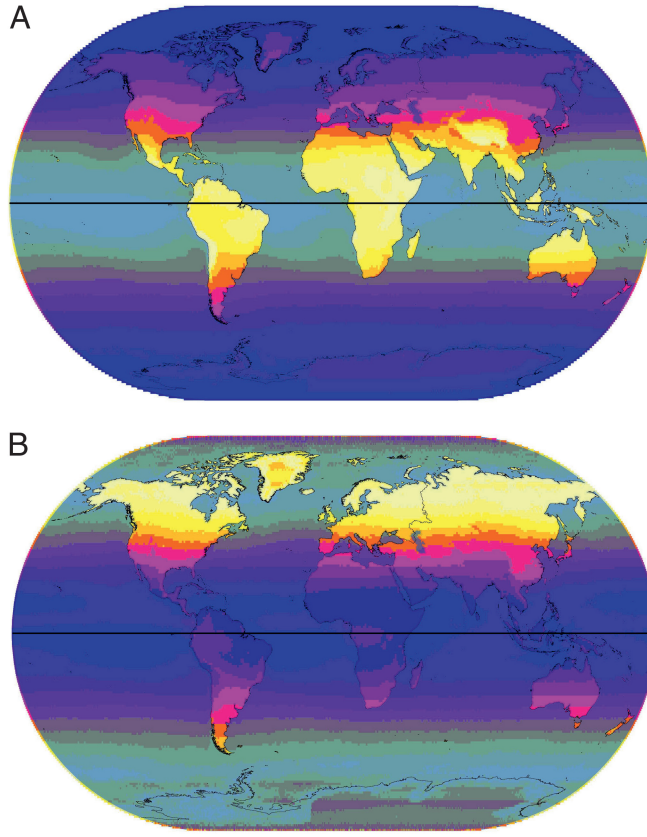


FIGURE 9.1 *(A)* Annual mean UVB (305 nm). Intensity is indicated by gradations from dark to light varying from 1 to 135 $J \cdot m^{-2}$ in 10 steps with oceans partially grayed-out. (*B*) Annual CoV for UVB (305 nm). Gradations of dark to light varying from 10 to 300 in 10 steps, with ocean area partially grayed-out.

Levels of UVA (Fig. 9.2*A*) are considerably higher than those for UVB. The latitudinal bands of UVA distribution are wider than those of UVB, and higher levels of UVA exist toward the poles. UVA at 380 nm is about 15 times more plentiful than UVB at 305 nm, with Western Europe receiving an average 283–570 $J \cdot m^{-2}$ of UVA compared to only 20–40 $J \cdot m^{-2}$ of UVB. Equatorial regions received slightly less UVA than tropical and subtropical areas. Albedo from lighter-colored ground and, especially, from snow increased the level of UVA; levels elsewhere were unchanged by atmospheric moisture. The pattern for the coefficient of variation in annual UVA (Fig. 9.2*B)* is nearly the inverse of that of UVB, and the rate

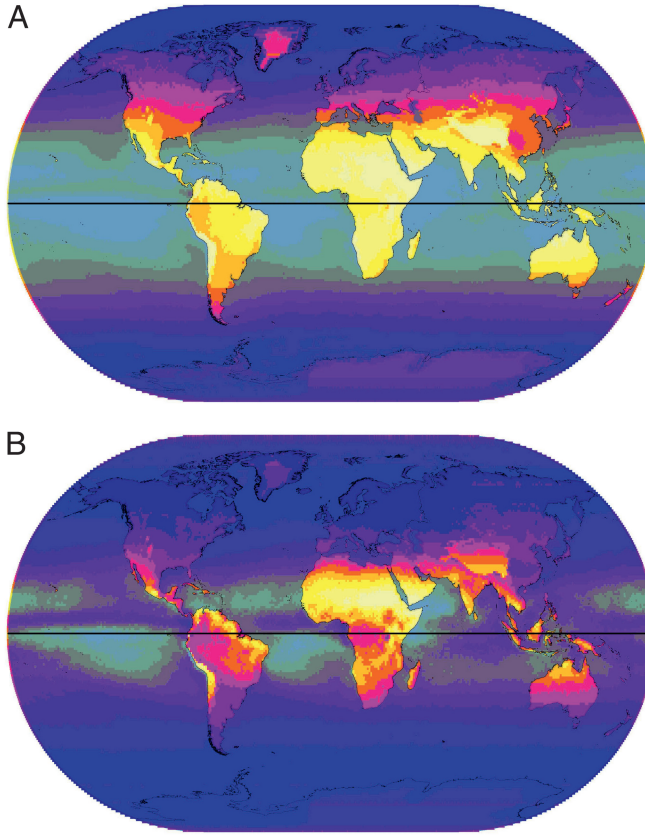


FIGURE 9.2 *(A)* Annual mean UVA (380 nm). Intensity is indicated by gradations from dark to light varying from 65 to 930 $J \cdot m^{-2}$ in 10 steps with oceans partially grayed-out. (*B*) Annual CoV for UVA (380 nm). Gradations of dark to light varying from 1 to 13 in 10 steps, with ocean area partially grayed-out.

of variation is approximately 1/200th of that of UVB. UVA varies mostly in dry tropical regions and exhibits low levels of variation away from the equator.

As a summary, it is useful to compare the patterns of UVR at the equator and within the tropics to those outside of the tropics. At the equator and within the tropics, average UVB is high, with two seasonal peaks at the equinoxes (Chaplin and Jablonski, 2009). Average UVA at the equator and within the tropics is also extremely high, but shows more variation in its intensity throughout the year. Outside of the tropics, average UVB levels are much lower and exhibit a single peak at the summer solstice (Chaplin and Jablonski, 2009). The extremely low average UVB in north-

ern Eurasia and North America is matched with a high CoV. [Note that there is no comparable, habitable, low-UVB land mass in the Southern Hemisphere (SH) except for the southern tip of South America (Chaplin and Jablonski, 1998).] Average UVA outside of the tropics is lower, but exhibits much less variation in its pattern. This indicates that loads of UVA throughout the year at these latitudes are lower but are more uniform throughout the year.

Within the time frames of hominin life spans and dispersals, solar regimes have been in flux. Solar irradiance and insolation are not static but vary according to different temporal cycles and scales. Insolation is tied to the degree and pattern of solar magnetic flux at or near the Sun's surface. Shorter wave insolation varies mostly as a result of energetic changes in the Sun's plage network and faculae (Brueckner, 1981; Fligge and Solanki, 2000). UVB levels vary by minute and day, as well as according to cycles of solar rotation (27 days) and the 11-year cycle of sunspots (Brueckner, 1981; Rottman, 2007); longer-term fluctuations occur over multiple decades and centuries. Total solar production varies only by 0.1–0.3%, but that of shorter wavelength UVR can vary by orders of magnitude more (Brueckner, 1981; Solanki et al., 2004). For instance, during the Little Ice Age (A.D. 1500–1800) the UVR levels are estimated to have been 10 to 4 times less than those of the present day (Solanki et al., 2004). Orbital parameters change the pattern of insolation in line with Milankovitch cycles of 22,000 years. Currently, SH experiences greater extremes, with intense insolation in the summer, and the Northern Hemisphere (NH) experiences less extremes and receives more insolation in the winter (Relethford, 1997; Chaplin and Jablonski, 1998). However, the land masses of the SH and NH have unequal annual means of insolation. Further, the distribution of land masses in the two hemispheres is such that a greater fraction of the SH receives high levels of UVR, whereas a greater portion of the NH receives extremely low levels (Chaplin and Jablonski, 1998).

## UV RADIATION AS A SELECTIVE FORCE IN THE EVOLUTION OF PIGMENTATION

UV radiation has been a potent and creative force in the evolution of life on Earth (Rothschild, 1999), and organisms have evolved a range of defenses against specific UVR wavelengths (Caldwell et al., 1998; Madronich et al., 1998; Agar and Young, 2005). As previously stated, naked skin was the primary interface between the human body and solar radiation throughout most of the history of the genus *Homo.* In equatorial Africa, members of the early genus *Homo* and, later, *Homo sapiens* were subjected to the potent mixture of UVA and UVB that prevails within the tropics throughout the year. UVA is plentiful and is capable of penetrating

deeply into the dermis of skin. UVB is more energetic and is less plentiful; it generally does not penetrate the dermis because it is absorbed and scattered. High-UVR environments generated strong selective pressures on the skin and human body (Table 9.1), leading to the evolution of permanently dark constitutive pigmentation, and the ability to increase eumelanin production in response to seasonal increases in UVB. This was accomplished genetically by positive selection leading to elimination of polymorphism at the *MC1R* locus and continued purifying selection acting on the same locus.

As humans dispersed away from the tropics, into southern Africa, and out of Africa entirely, they entered regions with lower annual average UVR (Jablonski and Chaplin, 2000; Chaplin and Jablonski, 2009) and significantly different seasonal mixtures of UVA and UVB. Two major changes in UVR regime were experienced by humans outside of the tropics. The first was the shift from high annual UVB with twin peaks of intensity at the equinoxes to generally lower annual UVB with a single annual peak at the summer solstice. The second was the steep decline in the duration and intensity of UVB exposure for every degree of increasing latitude (Chaplin, 2004; Chaplin and Jablonski, 2009), rendering much of the NH free of UVB for over 6 months per year. (The only exception to this rule was and is the Tibetan Plateau, which, due to its extreme altitude and thin atmosphere, receives much higher annual and summer levels of UVB than land masses at equivalent latitudes.) Reduced UVB levels and concomitantly reduced potential for cutaneous vitamin D biosynthesis generated positive selection for depigmentation. Hominins and modern humans dispersed independently many times into nontropical latitudes and evolved depigmented phenotypes by numerous and different genetically based means, some of which remain to be illuminated. It is important to stress that habitation of middle latitudes between approximately 23° and 46° involved the evolution of partially depigmented phenotypes capable of tanning.

## UV RADIATION AND THE EVOLUTION OF TANNING

Constitutive pigmentation is modified by tanning to produce facultative pigmentation. Tanning is an adaptation to seasonally high UVR, especially UVB, levels. Tanning phenotypes evolved many times in human history, probably as the combined result of independently acquired mutations on genes controlling the pigmentary system and of gene flow. Tanning comprises two mechanisms, immediate pigment darkening (IPD) and the delayed tanning reaction (DTR). IPD involves an immediate darkening of the skin following exposure to UVA, with maximum induction at 340 nm (Routaboul et al., 1999). The effect produced by IPD is transient and

TABLE 9.1 Summary of the Effects of UVA and UVB on the Human Body and the Selective Mechanisms Involved in the Evolution of Pigmentation

| Agent | Strength and Direction of Selection[a] | Proposed Selective Mechanism(s) |
|---|---|---|
| UVA | +++ | Photolysis of folate [as 5-methyltetrahydrofolate (5MTHF) in serum] directly and by ROS in the presence of flavins and porphyrins, resulting in reduction of folate available for cell division |
| UVA | ++ | Competition for folate: increased folate needs for DNA damage repair and as 1-carbon donor in methylation of DNA competing with folate needed for melanogenesis |
| UVA | ++ | Disruption of melanin production because of sensitivity of tyrosinase to high levels of ROS |
| UVA | + | Malignant melanoma (as the only skin cancer that causes death to individuals of reproductive age) |
| UVA | + | Photoconversion of excess vitamin $D_3$ to inactive metabolites |
| UVB | +++ | Production of cyclobutane pyrimidine dimers and damaged nucleotides requiring repair resulting from DNA absorption of photons; activation of folate-dependent DNA repair processes |
| UVB | + | Direct photolysis of folate (as 5MTHF in serum), reducing the amout of folate available for cell division and regulation of tyrosinase activity in melanogenesis |
| UVB | + | Competition for folate: increased folate needs for DNA damage repair and as 1-carbon donor in methylation of DNA competing with folate needed for melanogenesis |
| UVB | No effect | Sunburn |
| UVB | No effect | Damage to DNA and its repair system and alterations of the immune system lead to progressive genetic alterations and the formation of nonmelanoma skin cancers |
| UVB | - | Cutaneous photosynthesis of vitamin $D_3$ |
| UVB | - | Greater need for vitamin D in females probably causing increasing sexual dimorphism in pigmentation: exaggerated by sexual selection in some populations |

[a]The estimated strength of natural selection operating to darken and lighten pigmentation is indicated by numbers of " + " and "–" signs, respectively. See text for references for proposed mechanisms.

is visible on light skin as blotchy gray or bluish gray coloration appearing on sun-exposed surfaces. The cellular mechanisms of IPD are still poorly understood, but appear to involve both a spatial rearrangement of melanosomes within keratinocytes and melanocytes, along with photooxidation of existing eumelanin (Routaboul et al., 1999). Darker constitutive pigment phenotypes exhibit higher and more intense development of IPD (Routaboul et al., 1999). We suggest that the net effect of IPD is immediate absorption or scattering of UVR photons at a superficial level within the skin, thus sparing some damage to deeper layers.

Delayed tanning is what is normally thought of as tanning and is the process that results in facultative pigmentation. The DTR develops gradually over the course of several hours to several days or longer, depending on the duration of UVR exposure. UVA and UVB both induce delayed tanning, but the tans produced develop over different time courses and persist for different lengths of time (Suh et al., 2007). Delayed tanning involves the redistribution of melanin more toward the surface of the skin as in IPD, changes in the shape and intracellular location of melanin [such as the development of protective supranuclear caps of melanosomes over the nuclei of keratinocytes (Gibbs et al., 2000)], and increased de novo synthesis of eumelanin (Kollias et al., 1996; Tadokoro et al., 2005; Yamaguchi et al., 2006). Tanning affords only moderate protection against cellular damage from UVR (Sheehan et al., 1998, 2002) and, in fact, appears to be triggered by signals from UVR-damaged DNA. This is because of a protein 53 (p53)–mediated response to DNA damage caused by UVR leading to increased melanin production through increased synthesis of α-melanocyte stimulating hormone (α-Msh) (Miller and Tsao, 2009). From an evolutionary perspective, the importance of delayed tanning is that it is delayed, and that a "base tan" is slow to develop. Outside of tropical latitudes, the slow ramp-up of UVB in the spring to levels capable of inducing photosynthesis of previtamin $D_3$ provides a head start for vitamin $D_3$ production and storage before facultative pigmentation developed by the DTR competes for UVB photons in the skin. Under conditions of slowly increasing UVB, sunburns would have been rare and would not have posed a risk to survival or reproductive success. Early humans spent considerable time outdoors without clothing and were subject to gradual changes in UVR intensity and wavelength mixture with the seasons. They did not travel long distances away from home to go on vacation to sunny places nor did they go to tanning parlors. Tanning is viewed by modern clinicians as an imperfect adaptation to UVR because it damages the skin's connective tissues, immune system, and DNA, and thus leads to progressive changes resulting in skin cancer (Miller and Tsao, 2009). This is an appropriate statement for vagile and longevous 21st century humans but not for those of the 18th century or earlier who lived before

the advent of widely available, rapid long-distance transportation. With early reproduction and before the extension of the average human life span through improvements in diet and medicine, skin cancer had no effect on reproductive success. Further, the genetic pattern of skin cancer risk does not accord with predictions based on selection for resistance to skin cancer (Nan et al., 2009). In the context of human evolution, the evolution of tanning was a superb evolutionary compromise.

## CONCLUSIONS

The visualizations of UVB and UVA levels and variation presented here permit elaboration of the nature of the selective mechanisms involved in the evolution of variation in skin pigmentation and, notably, the evolution of tanning phenotypes in relation to seasonably variable levels of UVR. Skin pigmentation is probably one of the best examples of natural selection acting on a human trait. It is the product of two opposing clines, one emphasizing dark constitutive pigmentation and photoprotection against high loads of UVA and UVB near the equator (Figs. 9.1 and 9.2), and the other favoring light constitutive pigmentation to promote seasonal, UVB-induced photosynthesis of vitamin $D_3$ near the poles (Jablonski and Chaplin, 2000; Chaplin and Jablonski, 2009). Intermediate latitudes with their seasonally high loads of UVB favored the evolution of people with moderate constitutive pigmentation who are capable of tanning.

The time course for the elaboration of pigmentation within a human lifetime reflects its importance in human reproduction and, thus, in evolution. Human infants are born more lightly pigmented than adults and develop their genetically determined maximum level of constitutive pigmentation only in their late teens or early 20s (Robins, 1991) when they enter their period of peak fertility. The potential for development of facultative pigmentation also peaks during early adulthood. In middle and old age, constitutive pigmentation fades and the potential for tanning decreases due to a decline in the number of active melanocytes (Quevedo et al., 1969).

Skin pigmentation provides an attractive model system for understanding and teaching evolution and should be promoted as such. It is readily visible, and the basic mechanisms contributing to it are easily understood. Skin pigmentation fulfills the criteria for a successful evolutionary model. First, it was produced by an imperfect replicator. Pigmentation is determined by germline DNA, which is subject to mutation. Pigmentation is also subject to heritable variations in epigenetic transmission due to differential methylation of DNA and to extracorporeal memetic patterns of inheritance because of different cultural traditions. Second, there must be selection through differential survival of phenotypes. For skin pigmenta-

tion, this implies differential survival and reproduction rates of different phenotypes under different solar regimes. Lastly, natural selection must occur uniquely in time and space to give rise to isolating mechanisms. In the evolution of skin pigmentation, isolation was produced by distance and dispersion rather than sexual selection or other mechanisms. Thus, human skin is a perfect model to demonstrate the mechanism of evolution by natural selection in each of its required parts.

Considerable antagonism toward evolution is based on the common understanding of the word "theory" in its colloquial sense as a hunch. That the separate parts of the theory can be shown to apply fully to an easily understandable human trait should help further the acceptance of the "theory of evolution." Darwin's theory of natural selection can be likened to Newton's attempt to explain the movement of the planets in his "On the Motion of Bodies in an Orbit." Newton's effort gave rise to the *Principia Mathematica* and eventually to the Laws of Motion.

## METHODS

The UVR data used in this study were derived from readings taken from the NASA Total Ozone Mapping Spectrometer (TOMS), which was flown aboard the Nimbus-7 satellite between 1978 and 1993 (Herman and Celarier, 1996; http://toms.gsfc.nasa.gov/ery_uv/new_uv/). The data were collected and computed for pixels of 1° longitude by 1° latitude each; the solar flux was measured at or near local noon (Herman and Celarier, 1996). The readings were computed to account for the total ozone column and scene reflectivities (cloud and snow cover) in the same latitude-longitude pixel. The measurements were then combined with the results of radiative transfer calculations, terrain height, and solar zenith angle (Herman and Celarier, 1996). Single wavelengths representative of long-wave and medium-wave UVR were sampled by the TOMS. These were 380 nm for UVA (range 315–400 nm) and 305 nm for UVB (range 280–315 nm). The original dataset was very large and comprised over 64,800 readings taken each day from 1979 to 1992. Abridged datasets for each wavelength were produced by taking an average for all years, of the average of the 19th through the 23rd days of each month. The abridged datasets and coefficients of variation for both 380-nm UVA and 305-nm UVB were then mapped using ArcGIS. The strength of UVR at the ground varies by elevation, scene reflectivities, time of day, time of year, and factors influencing UVR absorption such as clouds. The TOMS apparatus takes all of this into account in calculating its readings. This means that many of the correcting factors that were used in latitude-based studies of estimated UVR at the Earth's surface were all accounted for in the one measure. Use of TOMS data thus obviated the need to correct for humidity, rainfall,

temperature, or elevation, as was done in previous studies (Roberts and Kahlon, 1976; Roberts, 1977). Using TOMS data has some advantages over using data collected by terrestrial-based recorders. This is because the TOMS apparatus does not "see" modern pollutants and so its records are more representative of the environment before industrialization than ground-based units that are "blinded" by low-altitude pollution. Further, the TOMS data used here were collected mostly before the 1990s, when widespread ozone depletion seriously affected UVR at the Earth's surface. The amount of ozone in the atmosphere decreased through the 1980s and caused a 3–5% increase in UVR in northern latitudes. This amount is insignificant for our purposes because it is comparable to natural variation in ozone concentration before ozone depletion. It is not necessary to model orbital parameters for the TOMS dataset because the data are direct readings and automatically compensate for orbital effects, something that latitude studies do not (Relethford, 1997).

# 10

# Footprints of Nonsentient Design Inside the Human Genome

JOHN C. AVISE

Intelligent design (ID)—the latest incarnation of religious creationism—posits that complex biological features did not accrue gradually via natural evolutionary forces but, instead, were crafted ex nihilo by a cognitive agent. Yet, many complex biological traits are gratuitously complicated, function poorly, and debilitate their bearers. Furthermore, such dysfunctional traits abound not only in the phenotypes but inside the genomes of eukaryotic species. Here, I highlight several outlandish features of the human genome that defy notions of ID by a caring cognitive agent. These range from de novo mutational glitches that collectively kill or maim countless individuals (including embryos and fetuses) to pervasive architectural flaws (including pseudogenes, parasitic mobile elements, and needlessly baroque regulatory pathways) that are endogenous in every human genome. Gross imperfection at the molecular level presents a conundrum for the traditional paradigms of natural theology as well as for recent assertions of ID, but it is consistent with the notion of nonsentient contrivance by evolutionary forces. In this important philosophical sense, the science of evolutionary genetics should rightly be viewed as an ally (not an adversary) of mainstream religions because it helps the latter to escape the profound theological enigmas posed by notions of ID.

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> The result of these cumulative efforts to investigate the cell—to investigate life at the molecular level—is a loud, clear, piercing cry of "design!" The result is so unambiguous and so significant that it must be ranked as one of the greatest achievements in the history of science. . . . The observation of the intelligent design of life is as momentous as the observation that the earth goes around the sun or that disease is caused by bacteria . . .
>
> Michael Behe (1996, pp. 232–233)

> Michael Behe's purported biochemical challenge to evolution rests on the assertion that Darwinian mechanisms are simply not adequate to explain the existence of complex biochemical machines. Not only is he wrong, he's wrong in a most spectacular way. The biochemical machines whose origins he finds so mysterious actually provide us with powerful and compelling examples of evolution in action.
>
> Kenneth Miller (1999, p. 160)

In *Darwin's Black Box*, biochemist Michael Behe (1996) issued a challenge to evolutionary biology by claiming that various molecular apparatuses within cells are "irreducibly complex" and therefore could only have been designed purposefully by a higher intelligence. There is no dispute that molecular systems can be astonishingly complex, but most geneticists attribute such biological complexity to the cumulative effects of evolutionary tinkering by natural forces (including a mindless directive agent, natural selection) rather than to conscious engineering by a supernatural entity. In support of this contention, evolutionary biologists have dissected the genetic mechanisms and the probable step-by-step phylogenetic histories by which complex biological features [including some that Behe deemed to be irreducibly complex, such as the eye (Gehring, 2005; Ayala, 2007), bacterial flagellum (Miller, 2004; Pallen and Matzke, 2006; Liu and Ochman, 2007), and biochemical gadgetry of blood clotting (Doolittle and Feng, 1987; K.R. Miller, 1999)] each could have evolved gradually from simpler precursor systems.

However, every year is witness to renewed pressure on textbook publishers and on state and local education boards to inject intelligent design (ID) into the science curricula of public schools. In recent decades, courts in the United States generally have ruled against such creationist initiatives on grounds that the government should not endorse particular religious beliefs (National Academy of Sciences and Institute of Medicine, 2008) (Table 10.1). The social pressures continue, however, not only from evangelical Christianity but from fundamentalist branches of some other religions, including Islam (Numbers, 2006; Hameed, 2008). This situa-

TABLE 10.1 Decisions or Excerpts from the Four Most Famous Courtroom Cases Involving Attempts to Mandate Creationist Instruction or Exclude Evolutionary Biology from Science Classrooms

| | | |
|---|---|---|
| 1 | Scopes "monkey trial," Dayton, Tennessee, 1925 | John Scopes was a high school teacher who admitted violating a state law that forbade the teaching in public schools of "any theory that denies the story of the Divine Creation of man as taught in the Bible." Three other states (Arkansas, Mississippi, and Oklahoma) likewise had passed laws prohibiting evolutionary instruction in public schools. The Tennessee court found Scopes guilty as charged. |
| 2 | *Epperson vs. Arkansas*, Supreme Court of the United States, 1968 | "Government in our democracy, state and national, must be neutral in matters of religious theory, doctrine, and practice. It may not be hostile to any religion or to the advocacy of non-religion, and it may not aid, foster, or promote one religion or religious theory against another or even against the militant opposite." |
| 3 | *Edwards vs. Aguillard*, Supreme Court of the United States, 1987 | The "primary purpose [of the Louisiana 'Creation Act'] was to change the public school science curriculum to provide persuasive advantage to a particular religious doctrine that rejects the factual basis of evolution in its entirety. Thus, the Act is designed either to promote the theory of creation science that embodies a particular religious tenet or to prohibit the teaching of a scientific theory disfavored by certain religious sects. In either case, the Act violates the First Amendment." |
| 4 | *Kitzmiller vs. Dover Area School District*, District Court for Middle Pennsylvania, 2005 | "ID [Intelligent Design] is not science and cannot be adjudged a valid, accepted scientific theory, as it has failed to publish in peer-reviewed journals, engage in research and testing, and gain acceptance in the scientific community. ID, as noted, is grounded in theology, not science. . . . Moreover, ID's backers have sought to avoid the scientific scrutiny which we have now determined that it cannot withstand by advocating that the controversy, but not ID itself, should be taught in science class. This tactic is at best disingenuous, and at worst a canard. The goal of the IDM [Intelligent Design Movement] is not to encourage critical thought, but to foment a revolution which would supplant evolutionary theory with ID." |

SOURCE: National Academy of Sciences and Institute of Medicine (2008).

tion evidences considerable global sympathy for ID (as well as profound misunderstandings about evolutionary biology by the public), no doubt exacerbated by the intuitive appeal of invoking a supreme intelligence to account for superb adaptations, such as the vertebrate eye. At a cursory level, fine-working adaptive traits are easy to rationalize; people of creationist persuasion need only invoke the attentive craftsmanship of a loving God, whereas the science-minded can invoke the unconscious agent, natural selection. Both a Creator God and natural selection are powerful shaping forces that might be expected to have engineered beautiful functionality and efficiency into complex biological features, such as the human genome. The much greater challenge—for proponents of ID and for scientists alike—is to explain complex biological traits that operate inefficiently or even malfunction overtly. On closer inspection, the human genome itself becomes a prime example of a highly complex trait with serious molecular shortcomings.

## THUMBNAIL HISTORIES OF THREE ANCIENT WORLD VIEWS

### Natural Theology and the Argument from Design

Before Darwin, most scientists, as well as theologians, accepted what seemed obvious: that divine intervention must have underlain nature's design. The standard "argument from design" traces back at least to the classical Greek philosopher Socrates (Sedley, 2008). Indeed, a common sentiment in recent centuries, and certainly in Western cultures, was that religion and biological inquiry were intellectual allies in a grand mission to explain, and thereby glorify, God and His Creation. Scientists and religious leaders often shared a conviction that the careful study of nature would confirm God's invention and oversight of life. Many scientists were avowed deists, and many clerics were also science-scholars, all jointly engaged in confirming God through rational inquiry (which frequently was seen as a helpful complement to traditional knowledge of God from gospel truths and religious revelations). When objections to science were raised in theology (and they often were), they usually stemmed from a notion that it was heretical or even dangerous (given a wrathful God) to strive to prove empirically that which required no proof: God's magnificence as detailed in the Scriptures.

In 1802, Reverend William Paley published an eloquent and thoughtful book (*Natural Theology*) that formally explained what many scientists of his era sought to accomplish in their studies of nature: proof and glorification of God's majesty through empirical investigations of His works. These biologists (i.e., natural theologians) typically started with two premises: that life's beauty and complexity were prima facie evidence

of God's creative power and that by carefully analyzing living nature, they inevitably would exalt God, and perhaps come better to comprehend His intentions. These themes were developed further in the ensuing *Bridgewater Treatises*, a set of eight works by different experts in biology, geology, and physics, published between 1833 and 1840. These books were commissioned by Reverend Francis Henry, Earl of Bridgewater, who died in 1829 but whose last will and testament encouraged and funded respected scientists to write treatises "on the power, wisdom, and goodness of God, as manifested in Creation."

Darwin himself was a natural theologian when he boarded the *HMS Beagle* in 1831. He later recalls in his autobiography that Paley's logic "gave me as much delight as did Euclid" and that it was the "part of the Academical Course [at the University of Cambridge] which . . . was the most use to me in the education of my mind." The 5-year journey on the *HMS Beagle* would prove to be a fateful voyage—not just for Darwin but for humanity—into previously uncharted waters in science and philosophy. Later, Darwin's elucidation of natural selection would launch a revolutionary paradigm in biology, wherein biological outcomes (species and the traits they possess) could be understood as products of natural forces (rather than the supernatural) that are entirely amenable to critical scientific analysis. The Darwinian revolution did for biology what the Copernican revolution three centuries earlier had done for the physical sciences: permit the workings of the universe to be interpreted as reflecting natural laws that could be studied and tested via objective scientific hypotheses, observations, and experiments (Ayala, 2008; Ayala and Avise, 2009).

## Creationism and ID

Creationism in its many guises is likewise an ancient human philosophy. Indeed, nearly all human cultures and religions have had their own creation mythologies: about life's origins in general and/or about human geneses in particular (Eliot, 1990; Avise, 1998). Natural theology (as described previously) and its offshoot, ID, have tended to be movements within Christianity, but many other cultures have held comparable sentiments about how a Creator God or Gods consciously manipulate the biological world. The modern ID version of natural theology can be dated to the publication in 1984 of *The Mystery of Life's Origin* (Thaxton et al., 1984). This project was encouraged by the Foundation for Thought and Ethics (FTE), a Dallas-based Christian organization. The book was intended to highlight difficulties with scientific explanations for life's origins; indeed, it claimed categorically that life could not arise by natural causes. The FTE soon sponsored a high-school textbook, *Of Pandas and*

*People* (Davis and Kenyon, 1989), that also took a hostile stance on the scientific evidence for evolution.

The ID movement got a media boost from the publication in 1991 of *Darwin on Trial* (Johnson, 1991), which, although anti-evolutionist in its stance, had a more serious aura of scholarship and did not tout hard-line creationist mantras (e.g., a young Earth, a universal flood) that were blatantly untenable scientifically. In that same year, a conservative think tank known as the Discovery Institute (DI) set up shop in Seattle. Since that time, the DI has largely supplanted the FTE as a primary hub of activity for the ID movement in North America. Another noteworthy publication in the ID movement was William Dembski's *No Free Lunch: Why Specified Complexity Cannot Be Purchased Without Intelligence* (Dembski, 2001). It echoes and purports to substantiate standard creationist claims that complex biological traits cannot emerge by natural evolutionary processes. However, the modern ID book with perhaps the biggest public impact is *Darwin's Black Box* (Behe, 1996), in which biochemist Michael Behe coined the term *irreducible complexity*. According to Behe, a cellular structure or other biological feature is irreducibly complex if the removal of any of its parts results in the loss of function. Such a structure, Behe claims, could not have evolved incrementally by natural selection but, instead, must have been engineered—in its entirety and for its current role—by an intelligent agent. That agent is left unspecified; however, the reference is clearly to God. Behe's arguments in *Darwin's Black Box*, although couched in unique language and metaphors and applied at a unique phenotypic level of biochemistry and molecules, essentially reiterate Paley's (1802) sentiments in *Natural Theology*.

These and other publications from the ID community have been refuted in the scientific literature, and it is not my intent here to repeat the voluminous evidence for how natural selection in conjunction with other nonsentient evolutionary forces can yield complex adaptations. Instead, my focus in this paper is on a relatively neglected category of argument against ID and in favor of evolution: the argument from imperfection, as applied to the human genome in this case.

## Theodicy

Theodicy (from the Greek roots *theós* for God and *dik* for justice) is the flip side or the dark side of natural theology. It is the formal term for philosophical attempts to vindicate God's holiness and justice in establishing a world that is rife with evils and woes. Throughout the ages, theologians have pondered why a loving and all-powerful deity allows human suffering. With respect to human phenotypes, why does God permit diabetes, heart attacks, hemorrhoids, impacted wisdom teeth, difficult childbirths,

or bad backs (not to mention behavioral flaws, ethical shortfalls, and death)? For some Christian denominations, an escape from this conundrum is to claim that such frailties result from humanity's fall from Grace in the Garden of Eden. Other religions have their own rationalizations. So, too, do the biological sciences. From a scientific perspective, biological imperfections in humans (and in other species) are an understandable byproduct of evolution by unconscious and uncaring natural forces. There are many solid scientific reasons why the biological outcomes of evolution by natural selection are expected to fall routinely short of designer perfection (Table 10.2).

TABLE 10.2 Some Reasons Why Evolution Routinely Yields Suboptimal Biological Outcomes

| | |
|---|---|
| 1 | Natural selection is a nonsentient process of nature, as uncaring and dispassionate as gravity. |
| 2 | Natural selection is not all-powerful. Instead, it is just one in a nexus of evolutionary forces, others of which can override the adaptation-promoting power of natural selection in particular instances, and thereby yield products that fall far short of designer perfection. |
| 3 | Random mutations, most of which are either deleterious or fitness-neutral, continually arise. |
| 4 | Harmful mutations (especially those that are only slightly deleterious individually) often fly below the radar screen of purifying natural selection, especially in small populations. |
| 5 | Genetic drift can alter the genetic composition of populations in ways that are uncorrelated with adaptive benefits. |
| 6 | Sexual selection on particular traits often operates in direct opposition to natural selection. |
| 7 | Genetic correlations and conflicts are common. In such cases, deleterious alleles linked to host-beneficial alleles at other loci can hitchhike with the favorable alleles, and thereby escape eradication by purifying natural selection, at least temporarily. |
| 8 | Pleiotropy and fitness tradeoffs are common. Thus, a particular genotype often has multiple phenotypic consequences, some of which benefit and others of which may harm the organism. |
| 9 | In sexual species, natural selection acts not only at the organismal level but at the level of genes. Thus, "selfish DNAs" (e.g., many mobile elements) can persist and proliferate in a genome without enhancing the well-being of a host population. |
| 10 | Phylogenetic constraints are ubiquitous. At any point in geological time, natural selection going forward can only work with the genetic diversity presented by lineages that have survived from the past. This places severe constraints on what evolution can achieve. |

Theodicy—and the associated "counterargument to design"—also have long histories (probably as ancient as the human species). In 1779, the Scottish philosopher-historian David Hume pithily captured the idea in a verbal exchange between two of his fictional characters in *Dialogues Concerning Natural Religion*:

> [Cleanthes]: The Author of Nature is somewhat similar to the mind of man, though possessed of much larger faculties, proportioned to the grandeur of the work he has executed. . . . By this argument alone, do we prove at once the existence of a Deity.
>
> [Philo]: What surprise must we entertain, when we find him a stupid mechanic.

Darwin himself was well aware (and at times seemed chagrinned) that biological imperfection was a powerful counterargument to ID. He wrote in chapter 14 of *On the Origin of Species by Means of Natural Selection* (Darwin, 1859):

> on the view of each organic being and each separate organ having been specially created, how utterly inexplicable it is that parts . . . should so frequently bear the plain stamp of inutility.

Darwin was also aware that biological evolution by mindless natural forces, in effect, could alleviate much of the theodicic paradox.

## THE HUMAN GENOME

In 2001, the first draft sequence of a human genome was published (Lander et al., 2001; Venter et al., 2001). It was about 3 billion nucleotide pairs in length, or roughly 50,000 times longer than the article you currently are reading (if each letter character or space can be equated to a nucleotide pair). The human genome that the researchers sequenced in 2001 was actually a composite of DNA sequences assembled from different people; however, collectively, it represented one "genome equivalent" from our species. In 2007, the full genome from a single person was sequenced in its entirety (Levy et al., 2007), and similar reports soon followed of whole-genome sequences from additional individuals (e.g., J. Wang et al., 2008; Wheeler et al., 2008). Recently, a Personal Genome Project was announced (Church, 2005), the goal of which is to use rapid DNA sequencing to gather numerous human genomic sequences. Such investigations are merely the latest generation of scientific inquiries into human genetics and biochemistry, which extend back about a century.

The age-old theodicy dilemma traditionally was motivated by human frailties at the observable levels of morphology and behavior. Do biological flaws extend to the molecular level also? Especially in the past half century, scientists have answered this question definitively, in the affirmative. Next, I will describe several complex features of the human genome that give compelling evidence for non-ID, and then I will close by highlighting some of the philosophical ramifications of these molecular discoveries. For a more comprehensive treatment of all these topics, see Avise (2010).

## FALLIBLE DESIGN: PROTEIN-CODING DNA SEQUENCES

By the early 1900s, doctors had begun to appreciate that biochemical malfunctions inside the human body can produce physical ailments and abnormalities. Archibald Garrod pioneered this revolutionary outlook in two path-breaking books: *Inborn Errors of Metabolism* (1909) and *The Inborn Factors of Inherited Disease* (1931). In *Inborn Errors of Metabolism*, Garrod detailed what then was known about the biochemistry and inheritance of four atypical human conditions: albinism, alkaptonuria, cystinuria, and pentosuria. Today, we know, for example, that alkaptonuria is a rare disorder (1 in 200,000 births) caused by a biochemical defect (in the degradation pathway for phenylalanine and tyrosine) that itself results from various mutational defects in a gene encoding homogentisic acid oxidase, which otherwise catalyzes the breakdown of homogentisic acid. As this acid accumulates, it binds irreversibly to collagen in the patient's body, eventually producing degenerative arthritis in the large joints and spine usually beginning in midlife. Before Garrod's time, this and many other disorders often were attributed to ethereal or mystical phenomena, such as bad karma or malevolent demons. After Garrod, the medical profession began to appreciate that careful scientific inquiry into metabolic disorders could reveal their mechanistic (genetic and biochemical) basis, and perhaps someday even lead to treatments or cures.

A modern analogue of *Inborn Errors of Metabolism* was launched in 1960 with the publication of *The Metabolic Basis of Inherited Disease* (Stanbury et al., 1960). The book has since seen more than half a dozen updated editions (at roughly 6-year intervals), and the title of the work also expanded to *The Metabolic and Molecular Bases of Inherited Disease* (*MMBID*), reflecting the recent explosion of DNA and protein sequence data. A recent edition of *MMBID* includes more than 6,000 pages in four volumes. In 255 chapters, each on a different heritable disorder or suite of associated genetic disorders, leading biomedical experts encapsulate current knowledge about the molecular mechanisms underlying inborn human diseases. They focus attention on the genetic basis of each disorder and also on the structure and function of each gene's protein product. More than 500 well-character-

ized genetic disorders are profiled in astonishing detail, and that number will only grow dramatically as the medical profession moves further into the genomics era. A plausible supposition is that at least some harmful mutations exist somewhere in the human species at each of the genome's ≈24,000 protein-coding loci.

The mutational defects profiled in *MMBID* occur in almost every operational category of protein, including enzyme-mediated energy metabolism, DNA/RNA processing, protein folding and degradation, molecular transport and secretion, signal transduction (mechanisms that link mechanical or chemical stimuli to cellular response), cytoskeletal elements, ribosomal functions, and structures and functions of exported (extracellular) proteins. Various mutations are known to debilitate the nervous system, liver, pancreas, bones, eyes, ears, skin, urinary and reproductive tracts, endocrine system, blood and other features of the circulatory system, muscles, joints, dentition, immune system, digestive tract, limbs, lungs, and almost any other body part you can name. With respect to age of onset, various genetic disorders appear in utero, from birth to the first year (the most commonly diagnosed class), from year 1 to puberty, from puberty to 50 years of age, or in seniors. Approximately two-thirds of the genetic defects described in *MMBID* shorten human life span, and about three-quarters of these cause death before the age of 30 years.

Another compendium of this sort, launched in 1966, is *Mendelian Inheritance in Man* (*MIM*) the current version of which describes thousands of human genes, of which more than 75% are documented to carry mutational defects associated with a disease condition. *MIM* has appeared in a dozen printed editions and now is also available online (*OMIM*), where it is updated regularly by computer-based literature searches. Yet another compilation of this sort is the Web-based Human Gene Mutation Database (HGMD) (Stenson et al., 2003), recent versions of which describe more than 75,000 different disease-causing mutations identified to date in *Homo sapiens*. More than 50% of these molecular damages involve nonsynonymous substitutions in protein-coding segments (exons) of genes, whereas the remaining molecular damages fall into a miscellany of categories, including large and small insertions or deletions of genetic material, DNA rearrangements, regulatory mutations in regions that flank a gene, and alterations in how particular mRNA molecules were spliced together. The HGMD is cross-referenced to *OMIM* and updated weekly. The HGMD provides a concise summary of all documented mutations that underlie a given metabolic disorder. For example, it describes 86 different disorder-causing mutations known in the glucose-6-phosphatase gene, 63 of which are nonsynonymous substitutions, 18 of which are small additions and/or deletions, 4 involve splicing anomalies, and 1 involves a regulatory region

flanking the coding sequence. Many further molecular details about each mutation are provided, as are electronic links to the original papers.

An apologist for the intelligent designer might be tempted to claim that such deleterious mutations are merely unavoidable glitches or secondary departures from a prototypical human genome that otherwise was designed and engineered to near perfection. As I will briefly describe in the next two sections, however, this excuse would be untenable, because all human genomes are also littered with inherent (endogenous) design flaws.

## BAROQUE DESIGN: GRATUITOUS GENOME COMPLEXITIES

For natural theologians in centuries past, as well as for adherents to present-day versions of strict religious creationism, biotic complexity is the hallmark—the unquestionable signature—of ID. However, gratuitous or unnecessary, biological complexity—as opposed to an economy of design—would seem to be the antithesis of thoughtful organic engineering. Yet, by objective scientific evidence, gratuitous and often-dysfunctional complexities (both in molecular structure and molecular operations) are so nearly ubiquitous as to warrant the status of hallmarks of the human genome. Here are some representative examples.

### Split Genes

The discovery in 1977 that standard protein-coding loci are split into coding regions (exons) interspersed with noncoding regions (introns) came as a complete surprise. So, too, did the discovery of large ribonucleoproteins known as spliceosomes, which biochemically remove the intron-derived segments from each premessenger (prem) RNA and then splice each gene's exons end-to-end to generate a mature mRNA. Approximately 1% of all known genes in the human genome encode molecular products that our cells employ to build spliceosomes and conduct splicing operations on premRNA. All this rigmarole has some advantages (e.g., opportunities for alternative splicing during ontogeny and exon shuffling during evolution, both of which can generate functional protein diversity), but such benefits do not come without major fitness costs.

There are good reasons to think that cells might be better off without introns, in an ideal world. Introns impose energetic burdens on cells. They are, on average, 30-fold longer than exons and are transcribed into premRNAs before being snipped out; thus, they probably extend the time to produce each mature mRNA by at least 30-fold (compared with the expectation for nonsplit genes). Even if time is not important for somatic cells, the metabolic costs of maintaining and replicating all the extra

nucleotides in introns must be considerable. To these cellular costs must be added the metabolic expense of making spliceosomes and running the extensive premRNA processing machinery. It can also be noted that many organisms (e.g., bacteria) do just fine without split genes and introns, as do the mitochondrial genomes within human cells; thus, there is no universal biological exigency that these features exist. Finally, the human nuclear genome would have ample room to house nonsplit genes for all the proteins it needs (including those that are now alternatively spliced) if an intelligent designer simply would jettison the genome's junk DNA (see beyond).

Nevertheless, for the sake of argument, let us assume that the metabolic costs imposed by introns are negligible. Do introns otherwise provide evidence of optimal genomic design? No, because premRNA processing also has opened vast opportunities for cellular mishaps in protein production. Such mishaps are not merely hypothetical. An astonishing discovery is that a large fraction (perhaps one-third) of all known human genetic disorders is attributable in at least some clinical cases to mutational blunders in how premRNA molecules are processed (Frischmeyer and Dietz, 1999; Philips and Cooper, 2000). For example, it has long been known that mutations at intron-exon borders often disrupt premRNA splicing in ways that alter gene products and lead to countless genetic disabilities, including various cancers and other metabolic defects (Krawczak et al., 1992). There is also good evidence that the number of introns in human genes is positively correlated with a gene's probability of being a disease-causing agent (López-Bigas et al., 2005). Avise (2010) summarizes many of the human genetic afflictions that have been documented (in particular clinical instances) to molecular errors in mRNA splicing at specifiable loci. These range from a variety of neurodegenerative diseases to debilitations of the circulatory, excretory, and other body systems. Many of these genetic disorders begin in infancy or early childhood; others are deferred to the elderly. The devastating symptoms of many such disorders, such as Lou Gehrig disease (amyotrophic lateral sclerosis), are simply horrible by any human standard.

### Gene Regulation and Nucleic Acid Surveillance

Each protein-coding gene or "structural gene" also has adjoining (*cis*) regulatory sequences that help to modulate when during development, and where in different tissues or organs, it is expressed. Most notable is a core promoter, usually several dozen base pairs long, to which suites of proteins known as transcription factors bind, to be joined by RNA polymerase molecules that catalyze the fabrication of premRNA from the adjoining structural gene. Other regulatory sequences called enhancers

and silencers, sometimes thousands of nucleotides upstream or downstream from the core promoter, further boost or inhibit transcription. Each gene may have several enhancers and silencers; these can be shared among genes, but different genes have different combinations. The enhancers and silencers influence transcription via their connections to large families of activator and repressor proteins that transpond regulatory signals to RNA polymerase via coactivators and other proteins. Distinct batteries of transcription factors and their molecular associates operate in different cell types, thereby helping to explain how different tissues and organs within an individual can have different patterns of gene expression despite sharing the same underlying genome.

Once a protein-coding gene has been turned on by appropriate regulatory signals, and mRNA has been transcribed, mechanisms of RNA surveillance spring into action. For any of a variety of reasons, some mRNA molecules become mistakenly truncated or otherwise blemished in ways that prevent their effective translation into a useful polypeptide. Somatic cells monitor for such defects and actively degrade many of the damaged mRNA copies. With respect to correcting genetic errors, RNA surveillance is the RNA-level analogue of the cell's many mechanisms for gene repair that operate directly at the level of DNA. Much of this makes good design sense; if DNA was not repaired routinely, or if faulty mRNAs were not destroyed, dysfunctional rogue proteins might appear in cells far more often than they do. However, if an intelligent designer is responsible for such repair mechanisms, he must also have presaged or understood that his original genomic design would include multitudinous flaws.

In a broad definitional sense, the genetic regulation of protein-coding genes can also occur at any posttranscriptional stage of protein production, including premRNA editing, the exportation of mature mRNAs from the nucleus, differences in the stability and transport of mRNA molecules after they have reached the cytoplasm, factors impinging on the translation process by which polypeptides are constructed from mRNA on ribosomes, polypeptide assembly into functional proteins, and posttranslational protein modifications or degradations. Many of these regulatory mechanisms involve complex biochemical pathways, and, collectively, they require major expenditures in cellular effort and molecular materials. Probably 50% or more of all coding genes in the human genome could be considered to play some direct or indirect regulatory role in development, for example, in cell signaling and communication, control over gene expression per se, or influences on cell division, structure, or motility.

Protein kinases provide a leading illustration of posttranscriptional regulation in eukaryotic cells. Kinases are enzymes that phosphorylate, and thereby alter the activity of substrate molecules. The human genome contains about 518 functional protein kinase genes that can be arranged

into several dozen functional families and subfamilies of loci, all of which arose, under an evolutionary interpretation, from successive gene duplication events across the long history of vertebrate animals (Manning et al., 2002). By altering the activity profiles of proteins, kinases exert regulatory control over numerous cellular processes, including metabolism, cell-cycle progression, cell movement and differentiation, physiological homeostasis, functioning of the nervous and immune systems, and signal transduction (mechanistic pathways by which chemical or other environmental stimuli evoke cellular responses).

Micro-RNAs (miRNAs) are another important class of loci involved in posttranscriptional genetic regulation (He and Hannon, 2004; Baek et al., 2008; Selbach et al., 2008). Each miRNA is a short (ca. 20-nucleotide) stretch of RNA that can bind to complementary sequences in the messenger RNA molecules of protein-coding genes, and thereby inhibit the translation or induce the degradation of specific genetic messages. Although the exact numbers and precise roles of miRNAs in the human genome remain to be illuminated, more than 500 such loci already are known and findings suggest that miRNAs might be major cellular tuners of protein synthesis. Another interesting class of molecules is long noncoding RNAs, each of which is typically hundreds or thousands of base pairs long (Petherick, 2008). Some geneticists posit that long noncoding RNAs will prove to be important regulators of gene expression; others demur on this possibility for now, pointing to countervailing evidence, such as the fact that cells seem to destroy long RNAs almost as soon as they are produced.

The various mechanisms described here thus help to orchestrate how particular genes and their protein products are expressed within a cell. Many additional routes to gene regulation exist, such as how nucleic acid sequences are spatially organized and packaged into chromatin fibers and chromosomes, how DNA molecules are complexed with histone proteins, and the pattern in which cytosine bases in DNA sometimes are modified via chemical methylation. In short, the sheer complexity of structure and function in the genetic regulatory apparatus of cells is not in dispute.

However, regulatory complexity during development is a double-edged sword for any organism. The molecular machineries of gene regulation are metabolically costly, and they often malfunction with disastrous health consequences. Improprieties in one or another aspect of gene regulation are responsible for many human ailments ranging from particular cases of asthma to various immune disorders, circulatory problems, and heart diseases. Many manifestations of cancer have been traced to aberrant methylation patterns in the promoter regions of particular genes (Jones and Baylin, 2002). Thalassemias—genetic disabilities that arise from inadequate supplies of oxygen-carrying globins in the blood—are another large class of metabolic diseases related to problems in gene regulation

(Weatherall et al., 1984). Protein kinases are also subject to disorder-producing malfunctions, with more than 160 different kinases having been implicated in cancers by their common association with particular tumor types and 80 kinases having been associated at least provisionally with various other disease conditions (Manning et al., 2002). Similarly, research suggests that occasional misregulation of miRNA molecules contributes to the total pool of human metabolic disorders, including perhaps DiGeorge syndrome as well as some cancers (Alvarez-Garcia and Miska, 2005).

Why an intelligent and loving designer would have infused the human genome with so many potential (and often realized) regulatory flaws is open to theological debate. Any such philosophical discussion should probably include the issue of whether the designer was fallible (and if so, why?). It should also address whether the designer might have recognized his own engineering fallibility, as perhaps evidenced, for example, by the DNA and RNA surveillance mechanisms that catch some (but not all) of the numerous molecular mistakes.

From an evolutionary perspective, such genomic flaws are easier to explain. Occasional errors in gene regulation and surveillance are to be expected in any complex contrivance that has been engineered over the eons by the endless tinkering of mindless evolutionary forces: mutation, recombination, genetic drift, and natural selection. Again, the complexity of genomic architecture would seem to be a surer signature of tinkered evolution by natural processes than of direct invention by an omnipotent intelligent agent.

**mtDNA**

Mitochondria are the only cytoplasmic organelles in humans to house their own DNA (mtDNA). A prototypical molecule of human mtDNA is 16,569 bp long. It is a closed circle of 37 maternally inherited genes, 22 of which encode tRNAs, 13 specify polypeptides, and 2 encode rRNAs.

Mitochondria are the primary seat of energy production in cells. The principal biochemical pathway in mitochondria by which this is carried out is oxidative phosphorylation, of which the respiratory chain is a key component. The respiratory chain consists of five enzyme complexes (I-V) plus coenzyme Q and cytochrome *c*. Complexes I and II oxidize NADH and succinate, respectively; complexes I, III, and IV pump protons to effect an electrochemical gradient; and complex V uses energy from that gradient to synthesize adenosine triphosphate from adenosine diphosphate. A remarkable fact is that four of these five enzyme complexes are composed of combinations of polypeptides from the mitochondrial and nuclear genomes (Graff et al., 1999). In complex IV, for example, 3 of the 13 polypeptides are encoded by mitochondrial loci (COI, COII,

and COIII), whereas the remaining polypeptides are encoded by nuclear genes. Only in complex II are all the necessary enzymatic subunits (four in this case) encoded by just one genome (the nuclear). Nuclear genes are also intimately involved in other basic mitochondrial functions. Indeed, mtDNA does not encode any of the proteins that are directly involved in its own replication, transcription, translation, surveillance, or repair. In short, mtDNA is just a tiny snippet of DNA that by itself would be absolutely helpless to itself and to the organism in which it is housed. None of this makes any biological sense, except in the light of evolutionary science (which has discovered that modern mitochondria are remnants of a microbe that invaded or was engulfed by a protoeukaryotic cell in an endosymbiotic merger that took place billions of years ago).

Like the other genetic systems we have considered thus far, the mitochondrial genome is plagued by mutations that often compromise molecular operations. Indeed, on a per-nucleotide basis, mtDNA experiences about 5–10 more mutations per unit time than do typical protein-coding nuclear genes (Brown et al., 1979). Many mtDNA mutations are of little or no consequence to a person's health, but many others have negative effects ranging from mildly debilitating to deadly. Clinical disabilities from mtDNA mutations disproportionately involve high-energy tissues and organs (Wallace, 2005; McFarland et al., 2007): brain, eye and other components of the peripheral nervous system, heart, skeletal muscle, kidney, and the endocrine system. Mutations in mtDNA have also been implicated in a spectrum of cancers (Copeland et al., 2002). In short, an emerging paradigm is that many of the degenerative diseases of aging have their etiologies in mitochondria, either as deleterious mutations in the mtDNA molecules themselves or as operational flaws in nuclear-mitochondrial interactions.

The serious health problems that arise from mtDNA mutations immediately challenge any claim for omnipotent perfection in mitochondrial design. Perhaps these mutational aberrations can be viewed as unfortunate but inevitable byproducts of molecular complexity. However, the intellectual challenges for ID go much deeper. Considering the critical role of cellular energy production in human health and metabolic operations, why would an intelligent designer entrust so much of the production process to a mitochondrion, given the outrageous molecular features this organelle possesses? Why would a wise designer have imbued mtDNA with some but not all of the genes necessary to carry out its metabolic role (and then put the remaining genes in the nucleus instead)? Why would a wise engineer have put any crucial genes in a caustic cytoplasmic environment in which they are exposed routinely to high concentrations of mutagenic oxygen radicals? Why would he have dictated that the mitochondrial genetic code must differ from the nuclear genetic code,

thereby precluding cross-translation between two genomes for which effective communication would seem to be highly desirable? Why would an intelligent designer have engineered mtDNA structures (e.g., closed-circular genome, no introns, no junk DNA, lack of binding histones) and mtDNA operations (e.g., little or no genetic recombination, production of a polygenic transcript, limited ability to mend itself, no self-sufficiency in transcription or translation) to differ so fundamentally from their counterpart features in the nuclear genome? In a nutshell, the underlying design of the whole mitochondrial operation seems to make no (theo)logical sense. Not only is the overall design of mtDNA suboptimal, but it appears downright ludicrous!

## WASTEFUL DESIGN: REPETITIVE DNA ELEMENTS

Before scientists gained direct access to DNA sequences from the modern tools of molecular biology, it was widely assumed that nuclear genomes were composed of sleek and efficient protein-coding genes strung together along chromosomes like tight beads on strings. In truth, however, structural genes have complex internal structures in which the exons typically are like small islands in much larger hereditary rivers of noncoding introns and regulatory regions. An even bigger surprise came with the discovery that the vast majority of human DNA exists not as functional gene regions of any sort but, instead, consists of various classes of repetitive DNA sequences, including the decomposing corpses of deceased structural genes and legions of active and retired transposable elements.

### Duplicons and Pseudogenes

At least 4,000 protein-coding genes and other lengthy stretches of DNA (up to 200,000 bp in length) are present not just once but in small to moderate numbers of copies per genome. At least 5% of the human nuclear genome consists of such gene families in which the redundant elements (termed *duplicons*, which arose through gene duplication processes) are typically more than 90% identical to one another in nucleotide sequence (Eichler, 2001; Bailey et al., 2002). Duplicate genes often perform useful functions, but we are concerned here with the evidence for genomic faults rather than benefits.

Because duplicate genes show close sequence similarity, they predispose chromosomes to pair abnormally during meiosis. Such homologous recombination can generate deletions, additions, inversions, or translocations of genetic material in the resulting gametes, which, in turn, can generate health problems in the resulting offspring. Metabolic disturbances

that result from duplicon-mediated genomic rearrangements typically stem from dosage imbalances attributable to the presence of too many or too few copies of a gene or to an altered orientation of particular genes relative to their regulatory regions.

Numerous metabolic disorders have been traced to duplicon-mediated recombination. No organ system seems immune to damage; various disorders are known to affect elements of the circulatory, respiratory, hormonal, skeletal, muscular, reproductive, excretory, or nervous systems. Some genetic conditions, such as red-green color blindness, are rather benign, whereas others, such as Prader-Willi syndrome, are severely debilitating. Many severe disorders tend not to be transmitted through families (because the afflicted seldom are able to reproduce) but, instead, recur in the human population from de novo mutations in paternal or maternal germlines. Approximately 0.1% of humans who survive to birth carry a duplicon-related disability, meaning that millions of people worldwide are afflicted by this category of metabolic errors. Many more afflicted individuals probably die in utero. Clearly, humanity bears a substantial health burden from duplicon-mediated genomic malfunctions.

### Mobile Elements

Perhaps the most surprising genomic finding of recent decades concerns the abundance of mobile elements. These stretches of DNA have—or previously had in many cases—the ability to colonize unique chromosomal locations by moving, replicatively, from one genomic position to another in a cell lineage. Incredibly, mobile elements constitute at least 45% of the human genome, and the true fraction is probably 75% or more if the tally were to include (*i*) processed pseudogenes that originated as a byproduct of mobile element activity (Esnault et al., 2000) and (*ii*) other intergenic DNA regions that probably originated long ago as mobile elements but are no longer identifiable as such because of postformational mutations.

Mobile elements have the potential to cause human diseases by several mechanisms. When a mobile element inserts into a host genome, it normally does so at random with respect to whether or not its impact at the landing site will harm the host. If it happens to land in an exon, it can disrupt the reading frame of a functional gene with disastrous consequences. If it jumps into an intron or an intron-exon boundary, it may cause problems by altering how a gene product is spliced during RNA processing. If it inserts into a gene's regulatory region, it can also cause serious mischief. The potential for harm by such insertional mutagenesis is great. It has been estimated, for example, that an *L1* or *Alu* mobile element newly inserts somewhere in the genome in about 1–2% and 5%,

respectively, of human births (Brouha et al., 2003; Cordaux et al., 2006). Another problem is that when a mobile element lands in a functional gene, genetic instabilities are sometimes observed that result in deleted portions of the recipient locus. Several genetic disorders have been traced to genomic deletions associated with de novo insertions of mobile elements (Chen et al., 2005). Finally, mobile elements (or their immobile descendents that previously accumulated in the human genome) can also cause genomic disruptions via nonallelic homologous recombination (Burwinkel and Kilimann, 1998). Serious metabolic disorders can result (Hedges and Deininger, 2007).

Despite the relatively recent discovery of mobile elements, the list of genetic disorders associated wholly or in part with their activities already is long. Still, any such list provides only a minimum estimate of these elements' collective toll on human health. This is because some of the most serious medical difficulties probably arise so early in ontogeny as to cause miscarriages that normally will remain of unknown etiology. Indeed, most mobile elements are especially active in the germline; thus, many of their deleterious effects probably register in gametic deaths and lowered fertility.

## A RECONCILIATION: EVOLUTION AS A SALVATION FOR THEOLOGY

From scientific evidence gathered during the past century, and especially within recent decades, we now understand that the human genome and the metabolic processes it underwrites are riddled with structural and operational deficiencies ranging from the subtle to the egregious. These genetic defects register not only as deleterious mutational departures from some hypothetical genomic ideal but as universal architectural flaws in the standard genomes themselves. The findings of molecular biology thus offer a gargantuan challenge to notions of ID. They extend the age-old theodicy challenge, traditionally motivated by obvious imperfections at the levels of human morphology and behavior, into the innermost molecular sanctum of our physical being.

Exactly how a fall from Grace in the Garden of Eden might have become translated into these molecular defects is mechanistically unclear (to say the least). How such genomic flaws arise and persist poses no insuperable mystery from the scientific perspectives of genetics and evolution, however. Herein, I suggest, lies a wonderful opportunity for nonfundamentalist religions.

Evolution by natural causes in effect emancipates religion from the shackles of theodicy. No longer need we agonize about why a Creator God is the world's leading abortionist and mass murderer. No longer need we

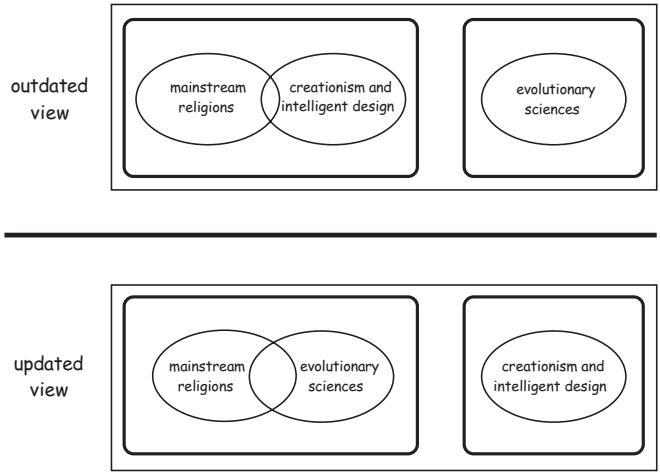


FIGURE 10.1 (*Upper*) Traditional placement of evolutionary biology as the odd-man-out to the spheres of mainstream religion and ID in many philosophical discourses about the human condition. (*Lower*) Unique and perhaps enlightened perspective in which ID is the odd-man-out to mainstream religions and the evolutionary sciences (whose spheres or magisteria may overlap to arguable degrees).

query a Creator God's motives for debilitating countless innocents with horrific genetic conditions. No longer must we anguish about the interventionist motives of a supreme intelligence that permits gross evil and suffering in the world. No longer need we be tempted to blaspheme an omnipotent Deity by charging Him directly responsible for human frailties and physical shortcomings (including those that we now understand to be commonplace at molecular and biochemical levels). No longer need we blame a Creator God's direct hand for any of these disturbing empirical facts. Instead, we can put the blame squarely on the agency of insentient natural evolutionary causation. From this perspective, the evolutionary sciences can become a welcome partner (rather than the conventionally perceived adversary) of mainstream religion (Fig. 10.1).

The evolutionary-genetic sciences thus can help religions to escape from the profound conundrums of ID, and thereby return religion to its rightful realm—not as the secular interpreter of the biological minutiae of our physical existence but, rather, as a respectable philosophical counselor on grander matters, including ethics and morality, the soul, spiritualness, sacredness, and other such matters that have always been of ultimate concern to humanity.

# Part III

## CULTURAL EVOLUTION AND THE UNIQUENESS OF BEING HUMAN

Darwin closed *The Descent of Man* by noting two fundamental aspects of the human condition that at face value might seem contradictory: "man with all his noble qualities, with sympathy which feels for the most debased, with benevolence which extends not only to other men but to the humblest living creature, with his god-like intellect— . . . still bears in his bodily frame the indelible stamp of his lowly origin." Ever since that time, philosophers as well as biologists have sought to reconcile these two sides of human nature, at times emphasizing our biological similarities and close evolutionary ties to other primate species, and at other times accentuating the features that seem to separate *Homo sapiens* from the remainder of the biological world. Indeed, some have argued that Darwin might better have entitled his treatise *The Ascent of Man*. Among the characteristics that might be deemed uniquely human are extensive tool use, complex symbolic language, self-awareness, death-awareness, moral sensibilities, and a process of cultural evolution that, while necessarily rooted in biology, goes well beyond standard biological evolution *per se*. Following the reasoning and terminology of the French philosopher Teilhard de Chardin, Theodosius Dobzhansky (1967) argued that two transcendent events have occurred to date in the Earth's history: the ancient emergence of life, which initiated the biosphere and enabled biological evolution; and the recent emergence of intelligence in *Homo sapiens*, which initiated the noosphere ("thinking arena") and enabled cultural evolution. In Part III of this volume, leading academicians with backgrounds ranging from genetics to linguistics and the

other humanities, reflect in diverse ways upon what it can mean to be uniquely human.

With respect to life-history traits, humans tend to live longer and mature later than our nearest living relatives (the great apes); yet, paradoxically, we share similar ages at which females lose the last of their fertility. In other words, human females have exceptional postmenopausal longevity. In Chapter 11, Kristen Hawkes addresses the history of scientific speculation about this evolutionary conundrum, including an elaboration of senescence theories, resource allocation theories, and especially the "grandmother hypothesis" that emphasizes the key supportive roles that postreproductive women can play in rearing grandchildren. Hawkes then focuses on life-history comparisons between humans and chimpanzees, and describes variation in aging patterns within and among populations of both species that may seem inconsistent with some of the standard assumptions of life-history theory, such as that tradeoffs inevitably exist between current and future female reproductive success. To help reconcile these apparent contradictions, Hawkes proposes that individuals differ substantially in their overall "frailties," such that those who are more robust can enjoy not only higher fertility but also better survival. Incorporating this idea into life-history theory may offer some fresh insights on human aging.

Culture, which can be defined as the deployment of socially learned information, has been a part of the "human condition" for more than 2 million years (as judged, for example, by the early appearance of stone tools) and it is the proximate reason for our remarkable success as a species. Cultural evolution emerged from biological evolution and the two processes are similar in some respects, but very different in others (such as in the speeds at which they operate and in their modes of information transmission). In Chapter 12, Peter Richerson and Robert Boyd develop the case that human genes and human culture coevolve, with cultural innovations often precipitating environment-mediated changes in natural selection and social selection with feedback effects on gene evolution. They further argue from paleontological and other evidence that gene-culture coevolution has been a dominant process underlying human evolution perhaps ever since the initial divergence of hominins from their last shared ancestor with the great apes. Looking forward, Richerson and Boyd see great promise for new genomic tools to help clarify gene-culture coevolution in several ways: by providing better marker-based assessments of human paleodemography; detecting genomic footprints of selection and thereby revealing exactly where and when selection took place in the human genome; and yielding mechanistic insights into the structures and functions of particular genes that have been under natural or social selection.

Culture and cultural evolution are greatly facilitated by another uniquely human characteristic: complex grammatical language, which allows people to share acquired knowledge, negotiate agreements, and otherwise interact readily in social contexts. The net result is that our ancestors were able to colonize a previously unoccupied "cognitive niche," one hallmark of which is enhanced survival due to environmental manipulation through cause-and-effect reasoning and social cooperation. But even if the evolution of general intelligence and the capacity for language are explicable in terms of the physical and social selective advantages they afforded our ancestors, the question remains as to why our evolved cognitive capabilities extend also to the kinds of abstract reasoning sometimes displayed in, for example, science, philosophy, law, government, and commerce. In Chapter 13, Steven Pinker reviews the history of speculation about the emergence of abstract intelligence, ranging from standard evolutionary scenarios for how physical and social evolution might have favored bigger brains, to supernatural causation (as was invoked by Alfred Russel Wallace, the codiscoverer of natural selection). Pinker then develops a somewhat different perspective on abstract intelligence that builds on a longstanding observation in linguistics: people often extend word constructions based on concrete scenarios to more abstract concepts, by analogy. Under Pinker's scenario of "metaphorical abstraction," cognitive schemas and social emotions that were important in promoting the capacity for language and adapting humans to the cognitive niche eventually became assembled into increasingly complex mental structures that have been co-opted to perform abstract mental functions they had not originally evolved to promote directly.

Language is again the topic of discussion in Chapter 14, where Terrence Deacon recounts a long history of oft-tortuous speculation about how a social capability that appears to be as complex and variable in expression as language might have arisen and come to occupy such a central position in human evolution. The basic problem, as Deacon and some others have seen it, is somewhat akin to explaining the emergence of other extravagantly complicated traits that in their initial evolutionary stages are not necessarily of clear utility to their bearers in the struggle for existence; indeed, one well-known modern linguist has argued that language competence did not evolve by standard natural selection because its rudiments would not likely have facilitated effective communication. In *The Descent of Man*, Darwin at one point resorted to the concept of sexual selection to explain the emergence of language, suggesting that human vocal complexity and the mental capacity it reflects might have evolved in part as a means to attract mates. On the other hand, even a prelinguistic symbolic communication or protolanguage could probably have contributed to a novel cognitive niche (see Chapter 13) that in turn

imposed novel selective demands on the proto-human brain and vocal apparatus for more effective communication. In any event, to add another perspective to the deliberations, Deacon suggests that a relaxation (rather than an accentuation) of selective pressures at the organismal level may have been the source of many of the complex and synergistic features of the uniquely human capacity for language.

High intelligence, cognition, and the capacity for reasoning that the human brain enables are so central to the human condition as to be inseparable from what makes us uniquely human. They are also highly adaptive features without which human culture could only be rudimentary at best. But is reasoning a single all-purpose procedure of the human mind, or, alternatively, is it an amalgam of special-purpose (i.e., "domain-specific") operations each having evolved in response to a specific suite of adaptive challenges posed by particular social or physical environments that were encountered routinely by our ancestors? The former hypothesis is sometimes referred to as the "blank-slate" theory of cognition in traditional psychology whereas the latter hypothesis tends to be favored by many evolutionary psychologists who envision the evolved architecture of the human mind to include multiple cognitive specializations each molded by natural selection to solve a particular adaptive problem. In Chapter 15, Leda Cosmides, Clark Barrett, and John Tooby review the history of these and other ideas about the nature of the neurocognitive system and human intelligence. Based in part on the results of psychological tests designed to distinguish experimentally between blank-slate and domain-specific operations of human cognition, the authors conclude that the human mind probably contains a multitude of different adaptive specializations for reasoning. One of the most salient of these specialized adaptations, the authors argue, is the hypertrophied human capacity to detect cheaters in social contracts.

Morality is a uniquely human attribute, to which Darwin attached a special significance: "I . . . 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." In the final chapter of these proceedings, Francisco Ayala makes a fundamental distinction between the *capacity for ethics* (i.e., the human capacity for a moral sense) and the expression of *moral norms* that can vary from one human society to another. The former, Ayala argues, is an inevitable byproduct of the biological evolution of high intelligence, which itself arose from selection pressures for other fitness-enhancing capabilities such as bipedalism and tool use; whereas the latter, by contrast, are products of cultural evolution rather than biological evolution. This distinction between morality and moral norms generally parallels the obvious distinction between the capacity for creative language and the particular languages that happen

to be spoken by particular societies. In developing this line of argumentation, Ayala invokes the distinction between an adaptation (something targeted quite directly by natural selection—in this case, higher intelligence) and an exaptation (something that arises by being co-opted to serve a positive role other than its original selection-promoted function). Ayala's distinction between ethics and moral norms is helpful but it nevertheless leaves open important questions regarding whether and to what extent particular moral norms (as well as a general moral sensibility) are genuinely adaptive for the human groups that display them (as opposed to being nonadaptive or perhaps even maladaptive on some occasions). Such questions no doubt will continue to intrigue sociobiologists and philosophers alike.

# 11
# How Grandmother Effects Plus Individual Variation in Frailty Shape Fertility and Mortality: Guidance from Human-Chimpanzee Comparisons

KRISTEN HAWKES

In the first paper to present formal theory explaining that senescence is a consequence of natural selection, W. D. Hamilton concluded that human postmenopausal longevity results from the contributions of ancestral grandmothers to the reproduction of their relatives. A grandmother hypothesis, subsequently elaborated with additional lines of evidence, helps explain both exceptional longevity and additional features of life history that distinguish humans from the other great apes. However, some of the variation observed in aging rates seems inconsistent with the tradeoffs between current and future reproduction identified by theory. In humans and chimpanzees, our nearest living relatives, individuals who bear offspring at faster rates do not cease bearing sooner. They continue to be fertile longer instead. Furthermore, within both species, groups with lower overall mortality rates have faster rates of increase in death risk with advancing age. These apparent contradictions to the expected life history tradeoffs likely result from heterogeneity in frailty among individuals. Whereas robust and frail alike must allocate investments between current and future reproduction, the more robust can afford more of both. This heterogeneity, combined with evolutionary tradeoffs and the key role of ancestral grandmothers they identify, helps explain aspects of human aging that increasingly concern us all.

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Long postmenopausal survival is a characteristic of our species. The use of life expectancy to compare human populations can obscure this fact because high infant and juvenile mortality kept all national life expectancies below 50 until the 20th century (Oeppen and Vaupel, 2002). As historical demography shows, girls that survived childhood usually lived long past menopause in previous centuries (Keyfitz and Fleiger, 1968). Hunter-gatherer survival curves are especially instructive (Howell, 1979; Hill and Hurtado, 1996; Early and Headland, 1998; Blurton Jones et al., 2002; Hill et al., 2007). They document characteristic human longevity in the absence of agriculture, public health institutions, and scientific medicine, all of which emerged long after the initial evolution of our species (Hawkes and Blurton Jones, 2005; Gurven and Kaplan, 2007). Distinctive and at first puzzling human postmenopausal survival was addressed in classic papers that used evolutionary theory to explain why living things grow old.

G. C. Williams (1957) laid out demographic reasons why declines in adaptive performance with increasing adult age emerge from the forces of natural selection. Because life is risky, cohorts inevitably diminish across adulthood. Consequently, the forces of selection weaken with age as fewer remain to be affected by it at older ages. Williams explained how the same forces result in different rates of senescence among species that reproduce more than once depending on two aspects of life history. First, when background mortality risk is lower, more individuals survive to older ages and selection against senescence is stronger. Second, selection against senescence is also stronger when the potential fitness-related payoffs to survivors increase with age. He illustrated the latter effect with the slow senescence of indeterminate growers that continue to increase in size and rate of egg production throughout adulthood.

Concluding that evolutionary life history theory predicts no post-reproductive period in normal life spans, Williams then addressed the apparent contradiction posed by survival past menopause in our own species by observing that older women still investing in descendants are not literally postreproductive. Hamilton (1966) mathematically modeled the tradeoffs nominated by Williams and demonstrated that the forces of selection shape mortality schedules to converge asymptotically with the age when reproduction ends. This process leaves, as Williams had surmised, few if any postreproductives. Because "much the best" (Hamilton, 1966, p. 27) demographic data are available on humans, Hamilton used a human population to explore the fit of observation with theory. This required him to explicitly confront the apparent discrepancy in the case of humans (Hamilton, 1966, p. 37):

> [T]he rather definite age of menopause seems conspicuously ignored by the as yet gently rising curve of the force of mortality. It is, moreover, a matter of common knowledge that the post menopausal woman normally remains a useful and healthy member of the community for some time. . . . [This] can be attributed to the beneficial effects of continued survival on the survival and reproduction of descendants. . . . In fact . . . the comparatively healthy life of the postreproductive woman . . . inevitably suggests a special value of the old woman as a mother or grandmother during a long ancestral period. . . .

Such a grandmother hypothesis, subsequently elaborated with comparative and phylogenetic evidence not available when the classic papers appeared, can explain not only the evolution of human longevity but other similarities and differences in life history between humans and the other great apes. We live longer; we take longer to mature but have shorter birth intervals; and we share common ages of terminal female fertility with the other great apes (Hawkes et al., 1998; Robson et al., 2006). The hypothesis focuses on females because as noted by both Williams and Hamilton our mid-life menopause is a central clue to human life history evolution and because the hypothesis employs E. L. Charnov's (1991, 1993) model of tradeoffs faced by females to explain mammalian life history variation. The forces of selection explored by Williams (1957, 1966), Hamilton (1966), Charnov (1993), and many other students of life history evolution (Stearns, 1992; Charlesworth, 1994) attend to fitness effects and not to proximate mechanisms, but T. B. L. Kirkwood's disposable soma model (Kirkwood and Rose, 1991) based on the same evolutionary tradeoffs between current and future reproduction has directed attention to processes of cellular maintenance and repair that affect somatic aging rates (Kirkwood and Holliday, 1979; Finch, 2007). Such processes likely have similar effects in both sexes, because longer-lived mothers pass on their cellular maintenance mechanisms to both sons and daughters.

I briefly summarize this elaborated grandmother hypothesis, then turn to patterns that initially seem inconsistent with the tradeoffs between current and future reproduction identified in evolutionary explanations for senescence. I focus on two apparent inconsistencies between theoretical expectations and empirical observations. First, theory predicts that current reproductive output should subtract from effort invested in maintenance for survival and reproduction in the future, yet individuals with higher fertility rates tend to continue bearing offspring to older ages; and in humans, women with later last births then survive longer afterward (Perls et al., 1997; Jacobsen et al., 2003; Emery Thompson et al., 2007; Gagnon et al., 2009). Second, theory predicts that lower adult mortality should slow rates of senescence, yet when populations of the same species are compared, the groups with lower mortality have steeper increases in death risk

with advancing age (Strehler and Mildvan, 1960; Gavrilov and Gavrilova, 2001). More survival to older ages makes senescence—measured as the pace of increase in age-specific mortality—appear to be faster. Heterogeneity of frailty within populations may explain these apparent contradictions (Hawkes et al., 2009).

J. W. Vaupel and colleagues (1979, 1998) proposed that heterogeneity in frailty might explain why the increase in mortality rates across adulthood begins to slow and even cease at advanced ages in humans and many other taxa. If individuals vary in their vulnerabilities to death, the more frail will usually die younger. Survivors to the oldest ages will therefore be a subset of the population enriched with individuals that had lower vulnerability all along. L. D. Mueller, M. R. Rose, C. L. Rauser, and colleagues (Mueller and Rose, 1996; Rauser et al., 2006; Rose et al., 2007) judged Vaupel's hypothesis to be in conflict with Hamilton's forces and found those forces themselves sufficient to explain the mortality plateaus. I argue here that rather than being mutually exclusive alternatives, heterogeneity of frailty and tradeoffs between current and future reproduction explain different things. Both are needed to account for salient aspects of fertility and mortality schedules in general, and those of humans and chimpanzees in particular. As Williams and Hamilton recognized, women usually outlive their fertility. This is not true of chimpanzees. Although childbearing ends at the same age in both species, only humans regularly survive for decades longer. Heterogeneity within populations can explain why this divergence in life history results in fertility schedules with different shapes.

## A GRANDMOTHER HYPOTHESIS

Anthropologists continue to debate the phylogenetic relationships among fossil taxa representing our ancestors and cousins (Wood, 2010), but genetic evidence unequivocally corroborates Darwin's hypothesis about our African ape ancestry (Glazko and Nei, 2003). The genera ancestral to our own are often characterized as bipedal apes (Wood and Collard, 1999), and chimpanzees are commonly used as a living model for the ancestors of our genus because they are genetically closest to us and similar in body and brain size to these extinct taxa (Robson and Wood, 2008). Correlations between life history traits and adult size across the living primates (Charnov, 1993) support the relevance of a chimpanzee model for the early members of our lineage.

Like other primates, chimpanzees feed themselves after weaning (Goodall, 1986). Systematic observations among modern hunter-gatherers show that human youngsters can be remarkably efficient foragers, acquiring large fractions of their own requirements at young ages (Blurton Jones

et al., 1997; Bliege-Bird and Bird, 2002; Bird and Bliege-Bird, 2005); but unlike chimpanzees, humans still depend on provisioning by others after weaning. Help is especially crucial for certain kinds of foods (Hawkes et al., 1995). Reliance on resources that young juveniles cannot handle effectively requires mothers to provision weaned offspring, but mothers nursing new infants provide less for their weaned children who receive subsidies from grandmothers (Hawkes et al., 1997).

The productivity of Hadza hunter-gatherer grandmothers especially in gathering hard-to-acquire staples, and the importance of their subsidies to weaned children with infant siblings (Hawkes et al., 1997), suggests a scenario about the ancestral past. An ecological change that reduced the availability of foods juveniles could handle independently would have opened a novel fitness window to older females without nursing infants of their own (Hawkes et al., 1997). By helping to feed weanling grandchildren, elder females would have allowed their daughters to bear the next baby sooner without affecting the survival of previous offspring. More vigorous elders, through greater reproductive success of their daughters, would have spread their slower somatic aging to more descendants. Longer adult life spans then reduced the cost of waiting longer to mature, delaying age at maturity and increasing adult body size (Hawkes et al., 2003). Because later births would interfere with grandmothering, selection would not have favored delaying ages of fertility decline. Increased allocation to somatic maintenance would have left less for current reproduction through the childbearing years, but subsidies from elders would have more than compensated, raising the fertility of childbearers (Hawkes, 2003).

We hypothesized that such a shift might have given rise to genus *Homo* (O'Connell et al., 1999; Hawkes, 2003) when drying environments and increased seasonality altered foraging opportunities for ancestral populations between 2 and 3 million years ago as forests shrank and grasslands spread across Africa (deMenocal, 1995; Bromage and Schrenk, 1999). Changes in body size and form are consistent with such a shift, as is the colonization of new habitats about that time. The hypothesis also helps explain the location of early archaeological sites and the composition of the faunal assemblages associated with them (O'Connell et al., 2002).

A formal model of the verbal grandmother scenario outlined here remains to be developed, but others have formalized links between the evolution of human longevity and the economic productivity of elders. H. S. Kaplan and A. J. Robson (2009) have shown that aging rates can be connected to the contribution adults make to juvenile survival. R. D. Lee (2003) has demonstrated that when intergenerational transfers of assistance are incorporated into a formal theory of senescence, it is the transfers instead of fertility that determine equilibrium aging rates. His simulations show that when elders transfer resources to close kin, mortality schedules

very like those observed in hunter-gatherers are maintained by selection against deleterious mutations (Lee, 2008).

## AGE STRUCTURES

Our grandmother hypothesis relies on Charnov's model of life history evolution (Charnov, 1991, 1993) to explain how correlated allometries in mammalian life history features apply to humans (Hawkes et al., 1998; Alvarez, 2000). Comparisons between other great apes and humans (Robson et al., 2006) have been essential in highlighting distinctive human life history features. As noted, chimpanzees are an especially important comparative model for phylogenetic, ecological, and morphological reasons. Fig. 11.1 shows the female side of the age structure for a human hunter-gatherer population and wild chimpanzees modeled from life tables.

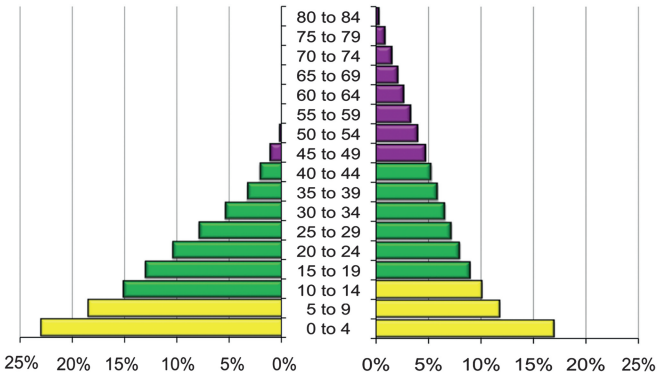


FIGURE 11.1 Female age structures modeled from life tables. Each bar shows the percentage of the population in the 5-year age class indicated in the vertical axis. Lightest bars, juvenile years; medium-gray bars, childbearing years; darkest bars, post-fertile years. Humans are on the right, represented by Hadza hunter-gatherers with Blurton Jones's (2002) data. In this population, life expectancy at birth is 33 years. With growth rate 1.3%/year, 32% of the women (those over 15) are past the age of 45. Growing populations are younger because more are born than die. If this population was stationary, the percentage of adult women past the age of 45 would be 39% (Hawkes and Blurton Jones, 2005). The left side of the figure represents the synthetic wild chimpanzee population constructed by Hill and colleagues (2000) using data from five wild study sites. Average age at first birth is 13 in wild chimpanzees so the 10- to 14-year age class is included in the childbearing years. Fertility ends by ~45 in both species. Less than 3% of the adult chimpanzees (counted as those over 10 years) are past the age of 45. The chimpanzee model assumes a stationary population.

The human example on the right in Fig. 11.1, the Hadza (Hawkes and Blurton Jones, 2005), is similar to other hunter-gatherers. Life expectancy at birth is <40 years, but a substantial fraction of adults are past the childbearing years. This is not true of chimpanzees, modeled on the left of Fig. 11.1 from the wild population synthesized from five wild study sites (Hill et al., 2001). Lower mortality in humans as compared to the other great apes has long been attributed to our propensity for cooperation and resource sharing (Sahlins, 1959), patterns that must surely affect death risks. The grandmother hypothesis highlights sharing by grandmothers in particular because, as noted by Hamilton, evidence that women remain healthy and productive past their fertility provides a clear link between human longevity and fitness payoffs to ancestral grandmothering. Sometimes elders survive with help from younger kin, but an evolutionary perspective predicts help to generally flow from older to younger relatives (Kaplan, 1994). Measures of strength and productivity among postmenopausal hunter-gatherers demonstrate their provisioning capacities (Blurton Jones and Marlowe, 2002; Walker and Hill, 2003). High fractions of maximum function through and beyond the childbearing years in humans contrast with the earlier geriatric declines of chimpanzees (Goodall, 1986; Finch and Stanford, 2004).

## DEMOGRAPHIC AGING RATES BETWEEN AND WITHIN SPECIES

As expected from Hamilton's model, age-specific mortality curves increase exponentially across adulthood (Mueller and Rose, 1996). This exponential increase was identified in human actuarial data by B. Gompertz in the early 19th century (Gompertz, 1825). A model bearing his name gives a fair fit to mortality data across a wide range of species (Finch, 1990):

$$m(t) = Ae^{Gt}.$$

Here $m$ is the mortality hazard rate, $G$ describes the rate of increase in adult mortality with increasing age ($t$), and $A$ represents age-independent adult mortality. Building on previous work by G. A. Sacher (1977), C. E. Finch (1990) labeled $A$ the initial mortality rate (IMR). Taking the natural log, the equation yields a line representing the logarithm of the hazard of death across adulthood with the log of the IMR as its intercept and $G$ as its slope. In the Gompertz model, differences in longevity between populations of the same species or between species can be due to differences in the initial mortality rate ($A$), differences in $G$ [or its transformed value, $\ln 2/G$, the mortality rate doubling time (MRDT)], or both. The slope ($G$), or the MRDT, is the demographic aging rate (Sacher, 1977). Across spe-

cies, lower initial mortality rates are correlated with shallower slopes and longer doubling times (Sacher, 1977; Finch, 1990; Ricklefs, 1998; Pletcher and Neuhauser, 2000).

Some have suggested that an MRDT of 7–9 years characterizes humans [e.g., Finch (2007, p. 12)], but MRDTs vary at least twofold across human populations (Hawkes et al., 2009). That variation among populations is correlated with variation in the initial mortality rate. However, the correlation is in the direction opposite from that predicted by a current vs. future reproduction tradeoff. Instead of the cross-species pattern identified by Sacher (Sacher, 1977; Finch, 1990; Ricklefs, 1998; Pletcher and Neuhauser, 2000), human populations with lower mortality levels ($A$) have faster rates of demographic aging ($G$). The age-specific mortality rate doubles more quickly, MRDT is shorter, when the age-independent risk of death ($A$) is lower.

This relationship, named for B. L. Strehler and A. S. Mildvan (1960), who first identified it across human populations, is robust and well described (Gavrilov and Gavrilova, 2001). Fig. 11.2 shows this Strehler–Mildvan correlation across a convenience sample of human populations chosen to represent a wide range of socioecologies and initial mortality rates [from Hawkes et al. (2009), with two Pygmy populations (Migliano, 2005) added here]. The figure is constructed from Gompertz models that were fitted to life tables for each population. Following Finch (1990) the models consider age-specific mortality risk from ages 30 to 80 [see discussion in Hawkes et al. (2009)]. The log of $A$, the hazard of death at age 30 (representing the IMR) is on the horizontal axis, and $G$, the slope of the log of the Gompertz curve is on the vertical axis. This correlation between the two variables across populations of the same species has also been found in widely diverse taxa where suitable data are available (Pletcher and Neuhauser, 2000; Gavrilov and Gavrilova, 2001). The limited data for chimpanzees are also plotted in Fig. 11.2. The synthetic chimpanzee population in the wild (Hill et al., 2001) used in Fig. 11.1 and the synthetic population from captivity (Dyke et al., 1995) represent variation in IMRs and demographic aging rates in that species. The same Strehler–Mildvan relationship found across human populations holds for chimpanzees.

## A HETEROGENEITY HYPOTHESIS

As noted, Strehler–Mildvan correlations across populations of the same species are opposite to those generally found in cross-species comparisons. Williams' (1957) verbal arguments, Hamilton's (1966) formal treatment, and Kirkwood's disposable soma model (Kirkwood and Rose, 1991) link lower mortality to stronger selection against senescence, and so slower rates of aging. Fig. 11.2 shows the opposite pattern. Within-species

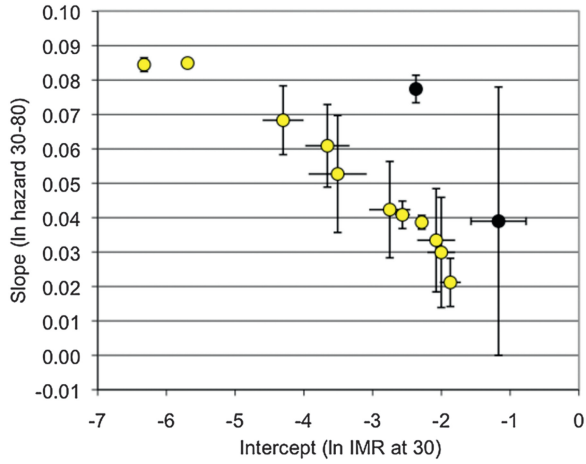


FIGURE 11.2 The slope of the log of the hazard of death from ages 30–80 by the log of the intercept at age 30 (IMR) taken from the values of *A* and *G* in Gompertz models calculated from life tables for a convenience sample of 11 human (open circles) and two synthetic chimpanzee populations (filled circles). See table 1 of Hawkes et al. (2009) for the values plotted here. The sample includes five hunter-gatherer populations, the United States and Japan to represent lower mortality levels falling in the upper left corner (the lowest IMRs and the steepest slopes), and two other cases to represent high-mortality populations depending on agriculture. Here, two pygmy populations from Migliano (2005) are added, the Aeta and the Batak. The chimpanzees are the synthetic wild population from Hill et al. (2001) and the synthetic captive population from Dyke et al. (1995). All life tables are female except for the !Kung and Agta, for which sexes were not distinguished in the original sources. Parameters were calculated on 5-year age classes, conditional on survival to the beginning of the age class preceding age 30. For the 11 human populations (yellow circles), the correlation between these estimates is −0.955.

lower mortality (lMR) is associated with a steeper increase in death risk across adulthood—faster rates of demographic aging. The evolutionary models all assume that more energy allocated to somatic maintenance pays off in future reproduction but leaves less for current reproductive effort. Life history variation among individuals of the same population often seems to go in the opposite direction as well. Women with higher fertility rates and later ages at last birth also have higher subsequent survival rates (Perls et al., 1997; Müller et al., 2002; Smith et al., 2002, 2009; Jacobsen et al., 2003; Gagnon et al., 2009). Such apparent absence of the expected tradeoffs within populations is a regular finding in field studies in animal behavior (van Noordwijk and de Jong, 1986; Pettifor et al., 1988; Lessels, 1991). A common explanation is that individuals differ in their resources.

When these differences are ignored (or unobservable) and subjects are pooled, the resource differences obscure the tradeoff because those with more resources can have more of everything. Like houses and cars (van Noordwijk and de Jong, 1986), more into mortgage payments leaves less for auto loans, but those with bigger budgets can put more into both.

If there is such heterogeneity, so that health and otherwise unobserved differences in frailty vary within the populations shown in Fig. 11.2, that heterogeneity could account for the Strehler–Mildvan correlations in the following way (Hawkes et al., 2009). Frail individuals die earlier. They die even earlier under more severe conditions. Such mortality selection (Manton and Stallard, 1984), or culling (Wachter, 2003), changes the relative representation of subpopulations among the survivors. Older age classes are a biased subset of younger ones and that bias affects their average mortality risk. In higher mortality populations of both humans and chimpanzees, older age classes are more strongly culled, leaving proportionately fewer frail survivors. Conversely, when background mortality is low, mortality selection is weaker and more of the frail survive longer. Although absolute risk of death is lower, the relative risk in each age class increases more steeply with advancing age because later age classes include more individuals with relatively greater vulnerability.

Heterogeneity could take many forms (Vaupel and Yashin, 1985). One simple possibility is that populations are composed of two (unobserved) subpopulations, each with a Gompertz schedule of risk. The frailer subpopulation has higher mortality risk at each age and steeper increasing risk. The log of the risk of death at each age has both a higher intercept and higher slope in the frailer subpopulation (Hawkes et al., 2009; Wilmoth and Horiuchi, 1999). Fig. 11.3 displays the age-specific mortality curves for simulated populations with such heterogeneity facing two different background conditions of mortality risk. In each condition there are two subpopulations, with exactly the same relative differences in age-specific risk of death. Gompertz demographic aging is linear with age on this semilog plot. The simulation uses observed ranges of variation in initial mortality rates and slopes across the sample of human populations in Fig. 11.2 to estimate realistic ranges. Fig. 11.3 shows the age-specific risk for the subpopulations and for the whole population when the subpopulations are pooled. More of the frail die at each age, and older age classes are increasingly biased toward the more robust in both conditions; but when overall mortality is low—the lower set of lines—more of the frail survive to older ages and so their higher and steeper risk has a larger effect on the relative risk of later age classes. The difference between the two subpopulations is identical in both environments, but the increase in mortality with age is about twice as steep when background mortality is lower. This is the same difference seen across empirical populations in Fig. 11.2.

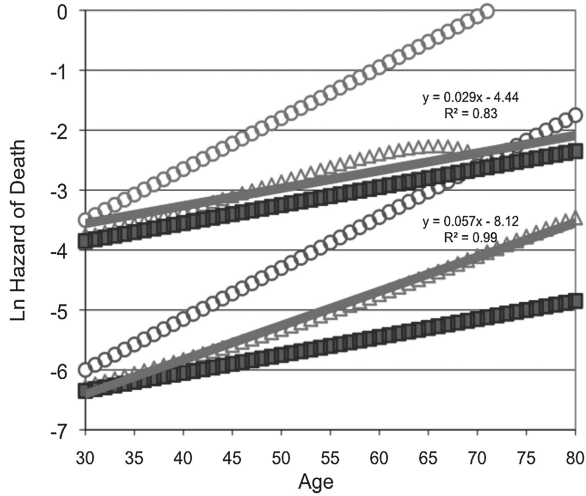


FIGURE 11.3 Two model subpopulations, one frail (open circles) and the other robust (filled squares), exposed to two conditions of age-independent mortality. Initial mortality rates are low (similar to the United States and Japan) for the lower set of lines and high (similar to Hadza hunter-gatherers) for the upper set of lines. Both subpopulations face Gompertz age-specific risk. Initial mortality rates for the two subpopulations differ by 0.35/year in both conditions with slopes of 0.03/year and 0.085/year, respectively. The simulations plot the age-specific mortality rate for the population pooled from these two subpopulations (open diamonds). The trendlines (single line described by the equations and correlation coefficients) measure how well the population mortality curves fit Gompertz models. The slope of the trendline is the demographic aging rate. For the population in the high-mortality condition, that slope is about half as steep as in the low-mortality condition. Relative size of the subpopulations at the initial adult age makes a difference. Here it is assumed to be the same at both high and low background mortalities because background risk is assumed to affect the frail proportion in two opposing ways. When age-independent mortality is high, so is the risk of early life tradeoffs that leave survivors more frail (see the discussion of early origins in the text). However, higher mortality also strengthens mortality selection across juvenile years, leaving a smaller fraction of the frail juveniles alive at maturity. On the other hand, when background mortality is low, fewer have faced early survival tradeoffs that increase frailty, making the frailer subpopulation smaller initially. Yet, weaker mortality selection across the juvenile years leaves more of the frail subpopulation surviving to adulthood.

## HETEROGENEITY AND FERTILITY

The same kind of differential frailty proposed to underlie the Strehler–Mildvan correlations in Fig. 11.2, and modeled in Fig. 11.3, is relevant to age-specific fertility. As shown in Fig. 11.1, the childbearing years end at the age of ~45 in both humans and chimpanzees. Like other female mammals, humans and chimpanzees build initial oocyte stocks in early life that then deplete with age (vom Saal et al., 1994). Most of the initial stock is lost to atresia, a continuing process of cell death that begins near birth. In women, stocks decline from ~7 million oocytes at 5 months after conception to <2 million at birth and ~400,000 at puberty (Baker, 1963). Only one in a thousand of those remaining when ovarian cycling begins actually ovulate. Numbers continue to fall across young and middle adulthood, reaching thresholds associated first with reduced fecundability, then secondary sterility, and finally menopause ~10 years after last birth. Average ages at these thresholds differ some across populations (Bentley and Muttukrishna, 2007) with substantial variation around the averages (Faddy and Gosden, 1996; O'Connor et al., 2001; Sievert, 2006; Broekmans et al., 2009). The classic counts of human ovarian follicle stocks show that among females of the same age, remaining primordial follicle stocks can vary by two orders of magnitude (Block, 1952; Richardson et al., 1987; Gougeon et al., 1994).

Chimpanzee follicle stocks also vary among individuals of similar age (Jones et al., 2007). Archived ovarian sections taken at necropsy from captive chimpanzees of ages 0–47 years index this variation and the declining numbers with age (Jones et al., 2007). Exponential regressions fit to the age-specific primordial follicle counts on those sections and also to the whole ovary counts across that 0- to 47-year range in the classic human datasets provide a quantitative comparison of follicular loss rate in the two species. The intercepts—the heights—of the two regression lines are necessarily different because the human data represent whole ovaries and only single sections were available for the chimpanzees. [An average section is ~1/2,000 of a human ovary (Block, 1952; Richardson et al., 1987)—likely the same for chimpanzees.] However, the rate of depletion with age measured this way, on these samples, across this age range, is indistinguishable between the two species (Jones et al., 2007). This similarity is consistent with a wider body of findings, including hormone and cycling data from captive chimpanzees (Graham, 1979; Gould et al., 1981; Lacreuse et al., 2008), suggesting they would reach menopause at about the same ages humans do—if they lived long enough (Walker and Herndon, 2008).

As implied by these similarities and noted above, humans and chimpanzees can give birth into their mid-forties but not beyond. However, in spite of this similarity in the end of the childbearing years (Fig. 11.1), the shapes of age-specific fertility curves in the two species are strikingly

different. Fig. 11.4 displays the average age-specific fertilities for three hunter-gatherer populations and the conservative age-specific fertility schedule synthesized from six wild chimpanzee populations by M. Emery Thompson and others (2007). Human populations can differ widely in fertility levels, but among them—hunter-gatherers included—the change in the rate of babies born to women of each age has a familiar peaked shape. "[I]n all populations where reliable records have been kept, fertility is zero until about age 15, rises smoothly to a single peak, and falls smoothly to zero by age 45–50" (Coale and Demeny, 1983, p. 27). The fertility schedule for wild chimpanzees is flat-topped instead. The rate reached before the age of 20 continues with little change for two more decades.

The percentages running along the horizontal axis in Fig. 11.4 show the relative size of each age class compared to the first age class of

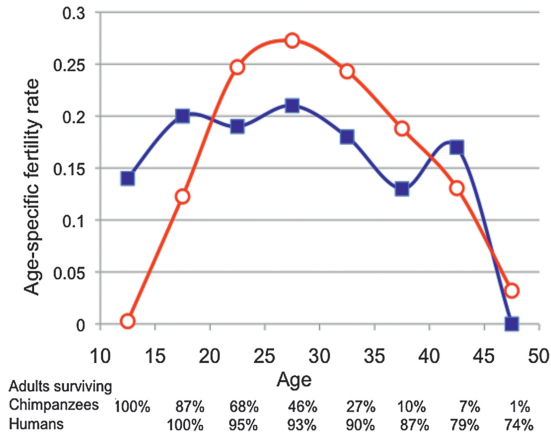


FIGURE 11.4 Age-specific fertility rates (ASFR) for humans and chimpanzees. Humans (open circles) are represented by the average of three hunter-gatherer populations: !Kung Bushmen of Botswana (Hill and Hurtado, 1996), Ache of Paraguay (Hill and Hurtado, 1996), and Hadza of Tanzania (Blurton Jones et al., 2002). Estimates for chimpanzees in the wild (closed squares) come from the conservative fertility schedule synthesized from six study sites by Emery Thompson et al. (2007). The bumps reflect small sample size (627 risk years in the initial chimpanzee adult age class declining to 8 risk years in the 45- to 49-year interval (Emery Thompson et al., 2007, supplementary table 2). The percentages along the horizontal axis indicate the proportion of those reaching adulthood that survive to the age class. The top row of percentages comprises estimates for chimpanzees from the number of risk years in each age class (Emery Thompson et al., 2007, supplementary table 2). They are just slightly lower than the model in Fig. 11.1 from the life table (Hill et al., 2001). The bottom row comprises human estimates from the female life table for Hadza hunter-gatherers (Blurton Jones et al., 2002).

adulthood. The chimpanzee figures come from the number of risk years observed in each age class in Emery Thompson and colleagues' (2007) supplementary table 2. For human hunter-gatherers the figures come from the female life table for Hadza foragers (Blurton Jones et al., 2002). As the percentages show, almost all of the chimpanzees that survive to adulthood then die during the childbearing years; only 1% do not. By contrast, 24% of the hunter-gatherer women die during the childbearing years; 76% do not.

Emery Thompson and colleagues (2007) demonstrated heterogeneity in chimpanzee fertility in their six-site sample by looking for associations between fertility rates and survival in females over the age of 25. They divided their observations into healthy and unhealthy years. An observation year for a given chimpanzee was considered healthy if she survived an additional 5 years or more, and unhealthy if she did not. Their figure 2 (Emery Thompson et al., 2007, p. 2152) shows that fertility in the thirties was about twice as high in females who would survive at least 5 more years than in those who would not. The finding indicates that mortality selection across the childbearing years culls the females with lower fertility. As the age classes shrink to almost nothing, they are increasingly biased to the less frail, more fertile females. Consequently, average fertility changes little even if the fertility of the survivors is declining relative to their own earlier rate.

We found similar heterogeneity in fertility in 19th century Utah women [the Utah Population Data Base (UPDB) (Bean et al., 1990)]. Although not hunter-gatherers, these women practiced natural fertility (Henry, 1961), so potential for continued childbearing is reflected by actual births. Individual records make it possible to investigate links between variation in fertility rate and age at last birth. Of 42,493 parous UPDB women born between 1849 and 1890, the 10,440 whose fertility ended before the age of 35 had fertility rates in the preceding years about half as high as the 2,695 women who would have last births after 45 (Hawkes and Smith, 2010). This parallels the chimpanzee variation with an important difference: all the women in the Utah sample, whatever their age of last birth, survived at least to the age of 50. The sample was restricted to women who lived at least to that age to avoid the confound of early last births due to early death (Hawkes and Smith, 2009). Subjects were also restricted to those married once and neither widowed nor divorced to reduce effects these characteristics may have on fertility.

Assuming that heterogeneity in fertility is similar in the hunter-gatherer women, this variation combined with the different survival schedules of humans and chimpanzees can explain the different shapes of the fertility schedules shown in Fig. 11.4. Most women, whatever their frailty, survive the childbearing years, whereas across those years mortality culls chim-

panzee females down to a least frail few. The human schedule is peaked because women with both high and low risk of fertility failure outlive the childbearing years. Beginning about the age of 30, each subsequent age interval contains more women who are past their last parturition. This drives down the average rate of baby production for later age intervals (Wood, 1989, 1994; Hawkes and Smith, 2010). The chimpanzee schedule is flat because heterogeneity in ovarian aging is culled away by mortality selection. Most chimpanzees die during the childbearing years and the survivors are females whose fertility rate has been high all along (Emery Thompson et al., 2007; Hawkes and Smith, 2010). In captive chimpanzees, lower mortality allows more frail individuals to survive longer so that captive chimpanzee fertility slopes down from a peak, more like the human pattern (Littleton, 2005; Roof et al., 2005).

## ORIGINS OF HETEROGENEITY IN EARLY LIFE

Human age structures looked much like the hunter-gatherer example shown in Fig. 11.1 until the 20th century when life expectancies at birth began to increase in some populations (Keyfitz and Fleiger, 1968; Oeppen and Vaupel, 2002). Until the mid-20th century, these increases were largely a consequence of decreasing numbers of dying infants and children: lower juvenile mortality is strongly associated with lower fertility. Fig. 11.5 shows number of births for UPDB women who survived at least to 50 by their own birth year across the 19th century (Hawkes and Smith, 2009). After the middle of the 19th century, fertility began a steady decline—falling to half of its earlier level by 1900. Fig. 11.5 also shows a concurrent change in adult mortality. The average age at death for women who had survived at least to 50 increased from ~75 at mid-century to ~80 at its end. These decreases in mortality and fertility typify changes in some other populations at about the same time, likely due to improvements in nutrition, sanitation, and medicine (Fogel, 2004; Finch, 2007). By the end of the 20th century, continuing decreases in fertility and increases in juvenile and adult survival resulted in life expectancies double those of most historical and ethnographic populations (Oeppen and Vaupel, 2002; Gurven and Kaplan, 2007; Finch, 2010). The increases in survival allowed increased heterogeneity at older ages. Other effects on heterogeneity are likely as well.

Associations between regional infant mortality rates and late life morbidities led D. J. Barker to propose his infant and fetal origins of adult disease hypothesis (Barker and Osmond, 1986; Barker et al., 1989; Gluckman et al., 2008). Those who survive nutritional and disease insults in early life are predisposed to metabolic and cardiovascular disease in adulthood. Pursuit of Barker's hypothesis has revealed that when historical cohorts

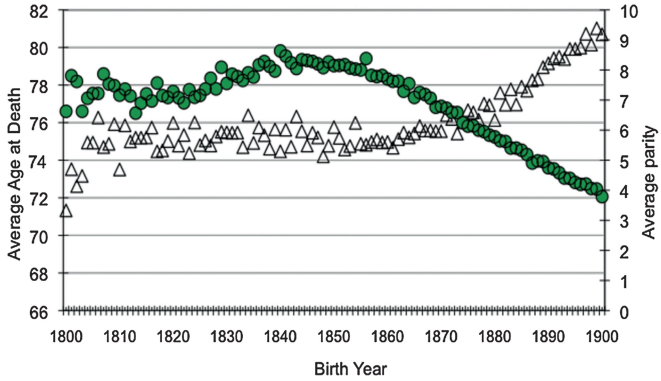


FIGURE 11.5 Number of births (filled circles) and age at death (open diamonds) in cohorts of UPDB women by their birth year across the 19th century, redrawn from Hawkes and Smith (2009)]. Only women who survived past the age of 50 are included.

have been exposed to famines and epidemics during fetal life they have higher rates of disease and mortality in later adulthood than do adjacent cohorts (Finch and Crimmins, 2004; Mazumder et al., 2009). Analyses of adult morbidity and mortality by birth month and season have yielded similar evidence of heterogeneity in frailty stemming from nutritional constraints and disease exposure in early life (Moore et al., 1997; Doblhammer and Vaupel, 2001).

Differences between cohorts are necessarily an underestimate of the likely heterogeneity. B. Mazunder and colleagues (2009) compared morbidities in later adulthood between Americans who were likely exposed in fetal life to the 1918 influenza pandemic and those in adjacent cohorts. As they noted, "Maternal health during the pandemic peak . . . varied widely from no clinical infection, mild uncomplicated flu or flu with severe secondary pneumonia that still permitted normal birth" (p. 4). Those whose birth dates indicate probable fetal flu exposure must include some unexposed individuals. In the same way, adjacent cohorts must include some individuals whose mothers experienced infection. Nutrition, energy expenditure, and stress may also impact the effects of disease (Finch, 2007; Kuzawa and Quinn, 2009; Kuzawa and Sweet, 2009), and recent disease history of groups in the sample may also influence responses to early life conditions (Costa et al., 2007; Pennington et al., 2009). Even with the imperfect association between exposure and birth date and effects of these unmeasured covariates, rates of cardiovascular disease after the age of 60 were >20% higher in those whose fetal development coincided with pan-

demic (Mazumder et al., 2009). That this is a minimum estimate of early life effects on heterogeneity in aging rates is underscored by longitudinal datasets documenting within-cohort associations between early growth and both ovarian aging and mid-life physical performance (Hardy and Kuh, 2002; Kuh et al., 2002).

The early origins hypothesis predicts that declines in mortality in the Utah women during the second half of the 19th century would affect the next generation. Longer survival likely indicates better nourishment, less illness, and reduced hardship. If so, the children of those surviving longer would have been less exposed to nutritional limits and infection in early life, and so have lower risks of various later morbidities. Improvements in nutrition, general public health, and, subsequently, medical interventions should mitigate early life insults and reduce consequent heterogeneity. However, lowered mortality also reduces mortality selection, allowing greater heterogeneity to persist to older ages. This heterogeneity hypothesis (Fig. 11.3) to explain population variation in demographic aging (Fig. 11.2) applies to chimpanzees (and other taxa) as well as humans. Life expectancy at birth for female chimpanzees in the wild is 15 years (Hill et al., 2001). In captivity it is 29 years (Dyke et al., 1995). This doubling of chimpanzee life expectancy is associated with reductions in rates of infection and nutritional stress (Goodall, 1986; Williams et al., 2008). In both chimpanzees and humans, improvements in nutrition and hygiene combined with medical interventions can double life expectancy. And in both, longer life expectancies are associated with faster rates of demographic aging (Fig. 11.2)—due perhaps, as argued here, to increased heterogeneity of frailty at older ages (Fig. 11.3).

## BACK TO GRANDMOTHERS

This heterogeneity hypothesis may explain why humans, chimpanzees, and other taxa display Strehler–Mildvan correlations. The similarities cannot explain why humans usually outlive the childbearing years and chimpanzees do not (Figs. 11.1 and 11.2). Physiological mechanisms, let alone genetic differences that underlie the survival differences, remain elusive (de Magalhães and Church, 2007; Finch, 2010), although mitochondrial mutation rates may be involved (Kujoth et al., 2007; Nabholz et al., 2007). Hamilton's forces (Hamilton, 1966; Rose et al., 2007) do not specify particular mechanisms of aging, but their incorporation in an analysis of human survival curves points to a deep history of reproductive benefits accruing to postmenopausal women in our lineage. Mueller, Rose, and Rauser have focused attention on the period of life in many species when mortality rates slow from an exponential increase and may become constant at succeeding age intervals. They reject Vaupel's heterogeneity of

frailty hypothesis (Vaupel et al., 1998) as a general explanation for these mortality plateaus, finding evidence more consistent with expectations from evolutionary theory about late life (Mueller and Rose, 1996; Rauser et al., 2006; Rose et al., 2007). When individuals survive past normal life spans, they are beyond the ages where senescence has been molded by ancestral forces of selection. "Hamiltonian theory predicts that late-life mortality rates should plateau and evolve according to the last age of reproduction in a population's evolutionary history" (Rauser et al., 2006, p. 26). Because human mortality rates begin to decelerate and depart from a Gompertz curve only around the ninetieth year (Vaupel et al., 1998), the mortality plateau criterion implies that contributions to reproduction from ancestral grandmothers continued through their eighties.

This demographic evidence of grandmaternal effects on reproduction in our lineage has other implications that can barely be touched on here. S. B. Hrdy (Hrdy, 1999, 2005, 2009; Burkart et al., 2009) has hypothesized that selection pressures for distinctively human cognitive and emotional capacities arose from our evolution as cooperatively breeding apes. Unlike our nearest living relatives, human mothers accept help with babies right from parturition. Depending on help, they can bear a new baby while previous offspring still need provisioning. This has consequences for selection pressures on both mothers and infants. Unlike chimpanzee mothers, humans must also consider the occupation and whereabouts of potential helpers as well as the needs of still dependent weaned children. Abilities to juggle these additional concerns supersede the more single-minded focus on the newborn of other ape mothers. The novel maternal sensitivities create problems in turn for human infants that do not arise for other infant apes. Human babies cannot count on mother's undivided commitment, so capacities to actively engage her and also to evaluate and engage other helpers are crucial. In high infant mortality environments, selection on those capacities would have been especially strong. Hrdy (2009) links those circumstance to the evolution in our lineage of motivations and capacities for intersubjective engagement that M. Tomasello and colleagues (Tomasello and Rakoczy, 2003; Tomasello et al., 2005) identify as the foundation for human prosociality.

Ethnographers have documented the ubiquity and importance of allomothering from many kinds of kin in living human communities (Sear and Mace, 2008), but grandmothers in particular are implicated in the hypothesis about the evolution of human life history entertained here. If ancestral grandmothers provided the help that initially allowed mothers in our lineage to move on to the next baby before the previous one could feed itself, propelling the evolution of human postmenopausal longevity, that initiated cooperative breeding in a previously independently breeding ancestral ape. These arguments link distinctive human cognitive and

emotional capacities to selection pressures that arose as a consequence of ancestral grandmothering.

Ovarian aging appears to differ little between modern humans and chimpanzees, making it likely the same pattern characterized our ancestors. Before the shifts to greater longevity in our lineage, heterogeneity in ovarian and somatic aging would have been strongly culled by mortality selection across the childbearing years. If grandmother effects reduced mortality across those years, heterogeneity in ovarian aging would have expanded as more and more women outlived their fertility. Subsidies for relatives' reproduction would have begun well before the average age at last birth, let alone the average age of menopause. By this argument, heterogeneity in ovarian aging is an ancient legacy of grandmothering in our lineage; but now such heterogeneity poses unprecedented concerns in the human populations where childbearing is delayed and nuclear families are isolated as never before. Many women find they have missed their own windows of fertility (Broekmans et al., 2009). Although aging is often seen as a process that befalls the old, evolutionary theories of aging predict that function begins to decline in early adulthood. Such declines have been documented not only in fertility, but in muscle strength and cognitive performance (Hunter et al., 2000; Salthouse, 2009); and where mortality levels have dropped to evolutionarily unprecedented lows, heterogeneity in somatic competence is increasingly well documented in those past mid-life (Mitnitski et al., 2005; Rockwood and Mitnitski, 2007). Just as grandmothering may have expanded heterogeneity in ovarian aging by lowering mortality across the childbearing years, recently dropping mortality rates at older ages expand heterogeneity well beyond them. As continuing innovations in medical and daily living technologies interact with mortality selection to produce complex dynamics in the health and welfare of elders (Manton, 2008), the heterogeneity in ovarian and somatic aging that is an aspect of our evolved life history becomes an increasing medical as well as social, economic, and political concern of our time.

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# 12

# Gene–Culture Coevolution in the Age of Genomics

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The use of socially learned information (culture) is central to human adaptations. We investigate the hypothesis that the process of cultural evolution has played an active, leading role in the evolution of genes. Culture normally evolves more rapidly than genes, creating novel environments that expose genes to new selective pressures. Many human genes that have been shown to be under recent or current selection are changing as a result of new environments created by cultural innovations. Some changed in response to the development of agricultural subsistence systems in the Early and Middle Holocene, including alleles coding for adaptations to diets rich in plant starch (e.g., amylase copy number) and for adaptations to epidemic diseases that evolved as human populations expanded (e.g., sickle cell and *G6PD* deficiency alleles that provide protection against malaria). Large-scale scans using patterns of linkage disequilibrium to detect recent selection suggest that many more genes evolved in response to agriculture. Genetic change in response to the novel social environment of contemporary modern societies is also likely to be occurring. The functional effects of most of the alleles under selection during the last 10,000 years are currently unknown. Also unknown is the role of paleoenvironmental change in regulating the tempo of hominin evolution. Although the full extent of culture-driven gene–culture coevolution is thus far unknown for the deeper history of

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the human lineage, theory and some evidence suggest that such effects were profound. Genomic methods promise to have a major impact on our understanding of gene–culture coevolution over the span of hominin evolutionary history.

The human cultural system supports the cumulative evolution of complex adaptations to local, often ephemeral environments. Using elaborate technology and depending on large bodies of cultural knowledge about plants and animals, stone-age foragers spread to a much wider range of habitats than any other mammal, from the frigid tundra in the Arctic to the arid deserts of Australia. The Polynesian outrigger canoe and the Arctic kayak are examples of the astoundingly sophisticated cultural adaptations that people have used to occupy distant corners of the globe. The forms of social organizations observed in humans are more diverse than the rest of the primate order combined. Humans constitute one of the world's most impressive adaptive radiations. We have occupied virtually every habitat on Earth by using technology and social organization to generate thousands of socioeconomic systems (Henrich and McElreath, 2003; Richerson and Boyd, 2005).

## CULTURAL EVOLUTION AND GENE–CULTURE COEVOLUTION

Culture has many definitions, but for our purposes a useful one is all of the information that individuals acquire from others by a variety of social learning processes including teaching and imitation (Boyd and Richerson, 1985). Transmission fidelity is often sufficiently high for culture to act as an inheritance system (Henrich and Boyd, 2002). We commonly observe that the ideas, practices, skills, attitudes, norms, art styles, technology, ways of speaking, and other elements of culture change through time, but we also see that persistent traditions exist. The English of Shakespeare is plainly a recent ancestor of the language spoken in England today, but modern English speakers cannot fully appreciate his plays without some knowledge of the differences between Elizabethan and modern English. Culture is thus a system of descent with modification. The idea that culture is fundamentally a kind of inheritance system that can be investigated using "population thinking" has been very productive. It led evolutionary theorists to model cultural evolutionary process by drawing tools and inspiration from fields as diverse as population genetics, epidemiology, ecology, game theory, and stochastic processes (Cavalli-Sforza and Feldman, 1981; Boyd and Richerson, 1985).

Those familiar with genetic evolution may be aided by considering some of the similarities and differences between genetic and cultural

evolution. Key differences include the nature of forces that act on cultural transmission, the observed patterns of transmission, and the relative rates of adaptation. Several of the forces that act on cultural variation to cause cultural evolutionary change include ones familiar to evolutionary biologists, such as random errors in teaching or acquiring items of culture (mutation), statistical effects in small populations (drift), and the effects on an individual's life chances as a consequence of using different cultural variants (natural selection). Other forces on cultural evolution are distinctive and derive from the fact that the acquirers of culture, even infants, are choice-making agents. People can to some extent pick and choose from among the different cultural variants they observe. Assuming their choices are not random, this creates a variety of bias forces that can be defined by how the choices are made (Richerson et al., 2003). Humans also selectively transmit variants that they have learned to their offspring and to others. We call such psychological processes "decision-making forces." Parent-offspring transmission dominates much (although not all) genetic transmission. In contrast, evidence on transmission patterns from a variety of sources indicates that individuals, including both children and adults, learn from a large, dynamic social network including parents, siblings, peers, and a wide range of others. The social learner uses biases that focus attention on those who tend to be same-sex, same-ethnicity, older, successful, prestigious, and available in order to accumulate a cultural repertoire from their social networks (Hewlett and Cavalli-Sforza, 1986; Henrich and Henrich, 2007; McElreath et al., 2008). Humans also generate new variants by nonrandom processes such as individual learning and creative thinking.

Field evidence on adaptive rates shows that they can be much faster for cultural evolution compared with genetic evolution (Rogers, 1995; Richerson and Boyd, 2005). For example, when American sweet potatoes tolerant of cool weather became available to the peoples of Highland New Guinea a few centuries ago, the new crop set off a population explosion and a spurt of parallel social and economic innovations in a number of Highland societies (Wiessner and Tumu, 1998). Attractive gadgets, such as mobile phones, have been taken up avidly around the contemporary world, and many of them lead to important knock-on cultural changes. The upshot of the differences between cultural and genetic evolution is that cultural evolution is inherently faster than genetic evolution.

Converging lines of evidence from many disciplines indicate that our psychological capacities for cultural learning evolved as an adaptation to temporally and spatially variable environments (Richerson et al., 2005; Herrmann et al., 2007). By adding bias forces and the transmitted effects of individual learning to random variation and natural selection, the cultural system can more rapidly track changing environments than can

genes alone, albeit at some considerable cost in maintaining a large brain to support the cultural system (Boyd and Richerson, 1985; Richerson and Boyd, 2001). Fast change also leads to large differences between neighboring societies, an important consideration for the evolution of human sociality (Richerson and Boyd, 2005). Even the most sophisticated social learners among other species, such as chimpanzees, are poor social learners compared with young children (Whiten et al., 2009). Recently, empirical investigations of cultural transmission and evolution have become common (e.g., Mesoudi, 2007; Efferson et al., 2008; McElreath et al., 2008; Bell et al., 2009) and much work in linguistics (Labov, 2001; Tomasello, 2008), applied psychology (Rogers and Shoemaker, 1971), and many other social scientific and historical investigations give convincing evidence of cultural evolution.

Cultures create novel environments that lead to new pressures from natural or social selection on genes (Richerson and Boyd, 2005). [We include here the effects of niche construction (Odling-Smee et al., 2003) insofar as modifications of the environment are rooted in culturally transmitted technology or social institutions.] To some degree, human culture is like any system of phenotypic flexibility. It has evolved to respond to environmental variation, allowing genes to be spared natural selection. Many elements of the biology of complex organisms such as humans act as mechanisms of phenotypic flexibility (Kirschner and Gerhart, 1998). For example, many developmental processes have an element of random variation and selective retention. Nerve axons grow prolifically and are pruned if they do not find appropriate targets. Like other systems for the inheritance of acquired variation, culture can play an active role in evolution through what is known as the Baldwin effect (Baldwin, 1896; Ghalambor et al., 2007). Systems for phenotypic flexibility, if they are adaptive, will generate phenotypes that tolerate small environmental changes and small genetic departures from current optima. Near selective optima, mechanisms of phenotypic flexibility shelter near-optimal genetic variants from selection. But away from selective optima, phenotypic flexibility has the opposite effect. By making survival and reproduction possible in novel environments, a system of phenotypic flexibility can expose genes to selection. Thus, presumably, the anatomically modern human populations that left tropical Africa to invade temperate and periglacial environments in Eurasia adapted first to them using clothing, shelter, and fire, but later also evolved husky physiques and lighter skin pigmentation adapted to cold temperatures and low light (Jablonski and Chaplin, Chapter 9, this volume).

Genes and culture resemble a symbiosis—two inheritance systems occupying the same physical body. The cultural partner can create complex adaptations rapidly compared with the genetic partner. As cultural adaptations became important, much could be gained from imitating a seemingly

successful idea or practice. If people can judge what is successful, or who is successful, new adaptive variation can rapidly spread through an entire population, sometimes within one generation. This ability might have been particularly important in glacial climates that were extremely variable on timescales ranging from a generation to a few tens of generations. Theoretical models suggest that such variation should favor the evolution of a cognitively costly system of cultural adaptation (Richerson et al., 2005). When variation has smaller amplitudes or longer timescales, selection causes genetic variation to track environmental changes at a lesser cost. When variation is strong at timescales of a generation or less, individual learning and other nontransmitted mechanisms for phenotypic flexibility will be favored by selection. The human genome and its associated biology provide a large brain, anatomic modifications for speech, and no doubt a large number of other genetically coded mechanisms that enable humans to host a fancy cultural system (Boyd and Richerson, 1985). At the same time, complex cultural systems will tend to adapt to genetically constrained cognitive capacities so as to be learnable and useful. Cultural adaptation to constrained cognition has recently been argued to be the case for language acquisition (Kirby et al., 2007) and reading (Dehaene, 2009).

Coevolutionists debate whether cultural evolution was largely controlled by selection acting on genes or whether cultural evolution often played the leading role during human evolution. For example, Wilson (1998) argues that epigenetic rules controlled cultural evolution until the latest Pleistocene or Holocene. In contrast, we have argued that cultural evolution has played a large role in shaping human genes. For example, group selection on cultural variation plausibly played a leading role in the evolution of genes underpinning our unusual social systems, including cooperative breeding and cooperation among distantly related individuals (Henrich, 2004a; Richerson and Boyd, 2005). Theory suggests that variation between groups can more easily be created in the cultural than the genetic system, and this prediction has some empirical support (Bell et al., 2009). Did natural selection first create capacities for culture for noncultural reasons after which cultural evolution began, as Ayala (Chapter 16, this volume) argues for systems of morality, or did culture commonly play leading roles in gene–culture coevolution, even in the evolution of the earliest hominins? Perhaps human nature itself is substantially a product of cultural evolution influencing human genetic evolution by a systematic, large-scale Baldwin effect.

## GENE–CULTURE COEVOLUTION IN HOMININ HISTORY

Wood (Chapter 1, this volume) provides an outline of human evolution. Studies of living apes [e.g., Whiten et al. (1999)] suggest that culture

has been at least a minor part of hominin capabilities since our last common ancestor with chimpanzees. Culture-led gene–culture coevolution thus potentially has a deep history in our lineage. Later, cultural evolution led to innovations in technology that, for example, made scavenging and hunting of meat productive. Ample meat and fat in diets, together with cooking, would have supported the evolution of larger, more expensive brains (Aiello and Wheeler, 1995; Gurven and Hill, 2009; Hill and Hurtado, 2009; Wrangham, 2009), leading to still-more sophisticated technology that eventually led to humans becoming specialized hunters of big game during the last couple of glacial cycles (Stiner, 2002). After 11,500 years ago, as the highly variable climates of the last ice age gave way to the much less variable climates of the Holocene, plant resources began to be exploited intensively in many parts of the world. Agriculture progressively became the dominant subsistence system in most parts of the world (Richerson et al., 2001). At the same time, human social organization was revolutionized. Evidence reviewed below shows that agricultural subsistence led to many genetic changes, but evidence regarding older episodes of coevolution is still scanty.

The idea that cultural variation fell under group selection at the scale of tribes is a modernization of a hypothesis first proposed by Darwin in the *Descent of Man* (Richerson and Boyd, 2004). Our last common ancestor with the other apes presumably had a social system based on dominance, with no provisioning of offspring beyond mother's milk. Cooperative breeding seems to have been essential to provide food supplements to mothers and juveniles to support the expansion of brains (Burkart et al., 2009). In anatomically modern humans, at least to judge by well-studied ethnographic examples, adult male hunters produced a large surplus of meat and fat that was channeled to women and children (Kaplan et al., 2000; Hill and Hurtado, 2009). To reduce the risk of big-game hunting, males cooperated in band-sized units including several good hunters. Bands were flexible units within a larger ethnolinguistic tribe from which bands drew members, partly but not entirely along kinship lines. As populations increased with the evolution of plant-intensive foraging and agriculture, population densities increased and social sophistication increased still further, leading to formal political systems (advanced chiefdoms and small states) by the Middle Holocene and to large states and empires in the classical period (Johnson and Earle, 2000). Somewhere along this trajectory of increasing social sophistication, humans developed a social psychology organized around culturally acquired social rules ("norms" to psychologists, "institutions" to sociologists) (Richerson and Boyd, 2008). People came to take on social identities that tied them emotionally to their social groups (Haslam, 2001). We became exquisitely sensitive to social boundaries symbolically marked by language, dress, ritual, and other stylistic differences between

"us" and "them" (McElreath et al., 2003; Henrich and Henrich, 2007, chap. 9, pp. 175–178; Kinzler et al., 2007; Shutts et al., 2009).

The paleoanthropological record is seriously deficient, as fossil records always are. Many forms of technology are very rarely preserved, including those made of wood, organic fibers, and leather. Usage wear on stone tools suggests that they were often used to make such products. Very rare finds, such as three aerodynamically sophisticated wooden javelins from an anaerobic deposit in Germany dating to 400 kya (Thieme, 1997), suggest that relying entirely on stone artifacts to deduce the technical sophistication of archaic humans is potentially misleading. Inferring the sizes of human populations from the paleoanthropological record is also difficult. Demography is important because cumulative cultural sophistication advances further and faster in large interconnected than in small isolated populations (Henrich, 2004b; Powell et al., 2009). Thus, human populations with identical spectra of individual cognitive ability can produce sophisticated or simple tools, depending upon effective population size. Exogenous controls on human populations from climate and competition with other species may be important. For example, in southern Africa between 70 and 80 kya, two short episodes with more sophisticated artifacts punctuate a long record with the less sophisticated Middle Paleolithic artifacts, perhaps because of population boom-and-bust events (Jacobs et al., 2008; Richerson et al., 2009). Immediately after anatomically modern humans left Africa, most populations seem to have been making Middle Paleolithic artifacts but, a short time later, the Upper Paleolithic peoples of western Eurasia made sophisticated tools and produced a large corpus of art (Foley and Lahr, 1997) of a complexity only observed in some of the most complex ethnographically and historically known foraging populations.

Thus, the four most obvious indices of human cognitive complexity, brain size, ability to colonize a wide range of environments, stone tool complexity, and artistic productions, are only very imperfectly correlated, for reasons that remain enigmatic. Inferences about past behavior and social organization are necessarily based on slim evidence. Some authors argue that even quite ancient hominins had modern behavior (Isaac, 1981). For example, Lovejoy suggests that the reduced canines of *Ardipithecus ramidus,* a form thought to be close to the last common ancestor with the other apes, indicate important social innovations very early in our lineage (Lovejoy, 2009). At the other extreme, Klein (2009, pp. 652–653) argues that at least one major social or cognitive modernization must have precipitated the exodus of anatomically modern humans out of Africa quite late in our evolutionary history. Both of these claims are controversial. Although the hypothesis that fast cultural evolution should have driven the gene–culture coevolutionary process is plausible on theoretical

grounds, the fact is that the large brain of anatomically modern humans *predates* the Upper Paleolithic cultural system by perhaps 150 kya. Perhaps chronically low population densities prevented the cumulative cultural evolution of highly complex tools and symbolic behavior that characterize the Upper Paleolithic and Later Stone Age (Powell et al., 2009). Favorable circumstances that allowed more substantial populations, particularly in western Eurasia after 40 kya and more generally in the Holocene, may have allowed anatomically modern humans to create highly elaborated cultures much along the line of Ayala's (Chapter 16, this volume) hypothesis about morality. Our hypothesis that culture was generally the leading rather than the lagging variable in the coevolutionary system may not always (or ever) be correct, even late in hominin evolution. Genomic data promise to have a large impact by shedding light on questions that are difficult to resolve with traditional methods.

## NEW GENOMIC TOOLS

Whereas paleoanthropologists will make slow progress in solving the many riddles hinted at in the preceding section, the genomics revolution, made possible by the rapidly falling cost of sequencing genomes, is providing important new tools. These methods promise two important contributions. First, they already help us to better understand paleodemography (Rogers and Harpending, 1992). Second, genomic methods can be used to estimate where and when selection has occurred in the human genome.

Mitochondria and autosomal lineage coalescence times record some evidence of past genetic bottlenecks. When population sizes are small, genetic diversity is lost by drift. If a population increases suddenly, as the hominin population did when anatomically modern humans expanded out of Africa, then a larger number of genes will have coalescence times indicating the time when the human population became large enough to sustain higher genetic diversity. Coalescence times are older for autosomes than for mitochondria or Y chromosomes in part because the effective population size for diploid autosomes is four times the size of the population of maternally transmitted haploid mitochondria or paternally transmitted Y chromosomes (Garrigan and Hammer, 2006).

Studies of the mitochondrial and autosomal genomes have given an interesting picture of the demographic expansion out of Africa. A succession of population bottlenecks caused decreasing genetic diversity farther away from our ancestral African homeland (Vigilant et al., 1991; Ramachandran et al., 2005; Liu et al., 2006; Handley et al., 2007; Wallace, Chapter 7, this volume). The populations most distant from one another, measured by the length of the most likely migration path from Africa, are most distant from one another genetically. Thus, the picture

of the genetic architecture of human populations derived from molecular methods bears a strong resemblance to that derived from classical human genetics (Cavalli-Sforza et al., 1994). Africans maintain the most genetic diversity, and the most distant migrants out of Africa retain the least due to successive bottlenecks. Selective sweeps and genetic drift have similar effects on the genome, so the most efficient estimation methods for dating selective sweeps are those which use selectively neutral variation to estimate population sizes and control for the effects of drift. The effects of selection on potentially nonneutral variation are then apparent as departures from expectations based on a neutral model (Rogers, 2001; Williamson et al., 2005). To this point, limitations in the size and nature of the samples of sequenced human DNA do not allow high confidence in either the population or selection reconstructions. The continuing fall in the costs of sequencing will increase sample sizes and coverage, and statistical methods will most likely continue to improve as well.

Sabeti et al. (2006) review the methods for detecting the action of selection on the genome on various timescales. On the longest timescales, selection is evidenced by functionally significant differences between species. For example, the *FOXP2* gene has two functionally significant differences between humans and chimpanzees. Preliminary sequences of Neandertal DNA suggest that we share these two changes with that species, thus placing the evolution of these changes before the separation of the two species several hundred thousand years ago (but see a discussion of problems with this interpretation below). Selective changes will show an excess of changes at sites that change amino acids of proteins compared with synonymous sites that do not. At shorter timescales, $\lesssim$250 kya, positive selection leaves a signature of reduced diversity in genes linked to the target of the selective sweep due to hitchhiking. Mutation and drift eventually restore this diversity, but in the meantime an excess of rare alleles in the linked region provides an estimate of the timing of the selective sweep. At timescales $\lesssim$80 kya, the linked region will contain an excess of derived alleles that have hitchhiked to high frequency along with the allele that was the target of selection. As human populations left Africa and became exposed to divergent selection in different environments and cultures, different alleles would have been swept to high frequency in different populations ($\lesssim$60 kya). Even if selection pressures are the same in different populations, and an allele with the same function is selected in different populations, the alleles in the different populations are likely to contain neutral differences in sequence. The *LCT* regulatory gene downregulates the secretion of lactase postweaning in most human populations. In western Eurasian and African dairying populations the gene is rendered nonfunctional, so that adults continue to secrete lactase and to benefit from lactose. Sequencing of the adult secretion variants of *LCT* from western

Eurasia and Africa revealed that they were dysfunctional in different ways (Tishkoff et al., 2007b). Finally, at timescales less than ≲30 kya, the linked hitchhiking region around the selected allele will not have been subject to recombination for a time-dependent length of sequence. The whole haplotype will be monomorphic for a certain distance. Thus, the *LCT* gene, which evolved after the evolution of dairying ~5,000 years ago, is associated with a long monomorphic haplotype. Recombination reduces linkage disequilibrium around the selected allele over time, providing a rough estimate of the time of the sweep.

Akey (2009) reviewed the promise and pitfalls of DNA sequence methods based on 21 genome-wide scans for alleles under selection. To assess the reliability of these methods, Akey compared eight genome-wide scan studies using the HapMap and Perlegen databases. The eight studies reported a total of 5,110 distinct regions under selection, but only 14.1% were identified in two or more studies and 2.5% in four or more. Nevertheless, he finds grounds for cautious optimism. First, many of the genes that occur in multiple studies have already been firmly identified as under selection, such as the *LCT* gene. Second, many of the genes under selection exhibit geographical differences. Because humans have recently spread from a tropical African homeland to the rest of the world, it is plausible that many genes have experienced divergent selection in the last 60,000 years. Evolution during this period is relatively easy to detect and many alleles under recent selection should be adaptations to the new local environments into which humans were dispersing. Significant issues remain. Some reflect the small and possibly nonrepresentative sample of genomes available for study. This defect will be remedied fairly rapidly. Statistical methods for detecting selection are also likely to improve dramatically (Grossman et al., 2010). A deeper difficulty is the lack of understanding from genomics alone about the phenotypic effects of the genes that selection has targeted. In the case of genes with strong and direct phenotypic effects, such as *LCT, HBB* (the sickle cell gene), other genes coding for resistance to malarias, skin pigmentation genes, and a few others, a functional understanding of the genes preceded genomic analysis, which has added only wrinkles to the classic stories. Presumably, many of the genes under selection are quantitative trait loci in which selection for a given phenotype will exert weak selection at many loci. Functional annotations for genes that are transcribed into proteins give only general hints about the function of the particular alleles that have been selected in the human lineage. We do not seem to have any substitute for functional studies targeted on sequences that have apparently undergone recent selection to understand why they might have come under selection. To advance rapidly on a broad front will require the same sorts of high-throughput methods that have revolutionized genomics also be applied to the expression of genes during develop-

ment, on the model of ChIP-on-chip technology, which is still in its infancy as far as vertebrate epigenomics is concerned.

Studies of the *FOXP2* gene provide a cautionary tale, exemplifying our still-primitive understanding of the connection between genotypes and phenotypes (Coop et al., 2008; Fisher and Scharff, 2009). This gene, coding for a regulatory protein, has apparently been under strong selection since the last common ancestor with the other apes. Two amino acid substitutions have taken place in the hominin lineage. Early reports from a study of language deficits in a family with a rare *FOXP2* mutant suggested to some that it is a grammar gene. However, it turns out to be a highly conserved gene that is expressed in a wide variety of tissues during vertebrate development. In the brain, a ChIP study shows that it down-regulates *CNTNAP2,* the gene encoding contactin-associated protein-like 2, a member of the neurexin superfamily. This gene is involved with cell recognition and cell adhesion, playing a role in nervous system development, including in the human frontal cortex during mid-development. Hence, it is expressed in tissues that may well relate to language abilities. However, other studies identified several *hundred* other potential targets of *FOXP2* as though it plays a role in many regulatory circuits during development.

The timing of the evolution of the common human *FOXP2* allele has also proven perplexing. The region near the substitutions in the derived human gene contains a high frequency of derived neutral variants that have not been disrupted by recombination, suggesting that the second of the two human substitutions on the gene must have taken place in the last 130 kya (Coop et al., 2008). On the other hand, Krause et al. (2007) sequenced Neandertal DNA and recovered the same genotype as modern humans, implying that the modern human allele evolved more than 300 kya. Several hypotheses have been proposed to explain this puzzle. They include (*i*) laboratory artifacts, *(ii)* introgression between Neandertals and anatomically modern humans (Plagnol and Wall, 2006), and *(iii)* the possibility that the two amino acid substitutions are ancient, and that the linkage disequilibrium observed in modern humans arose from recent selection on a nearby gene rather than on *FOXP2* itself (Coop et al., 2008; Ptak et al., 2009). Thus, although the promise of genomics and related high-throughput techniques to study human evolution is high, human biology, evolutionary history, and extant population structure are all intimidatingly complex. Not every problem will be quickly solved, and many analytical improvements are needed.

## THE EXTERNAL SELECTIVE ENVIRONMENT

The role of culture in adapting to temporal and spatial environmental variability has long been an important theme in gene–culture coevolu-

tion theory (Potts, 1998; Richerson and Boyd, 2000; Wakano et al., 2004). Environmental change over the course of hominin evolution has been substantial. Climate variation correlated with variations in Earth's orbit has progressively increased and shifted from the dominance of the 23-kyr (precession) cycle in the Miocene and Early Pliocene to the dominance of the 41-kyr (tilt) cycle from the Middle Pliocene through the Early Pleistocene, and finally to the dominance of the 100-kyr cycle (eccentricity) during the Middle and Late Pleistocene. The Middle Pliocene shift roughly correlates with the appearance of our genus, *Homo,* and the evolution of progressively larger-brained and technically more sophisticated humans occurs after the mid-Pleistocene shift (deMenocal, 1995). Variation on the orbital timescales (900+ human generations) probably has little direct impact on the gene–culture system. The higher-frequency components of climate variation, which are perhaps correlated with the lower-frequency orbital scale fluctuations, are likely to be much more important. High-resolution ice cores from Greenland first revealed that high-frequency, high-amplitude submillennial and millennial variation (1–100 human generations) occurred during the last ice age (Ditlevsen et al., 1996). Long high-resolution ocean cores suggest that the tempo of this variation has increased over the last four cycles (Martrat et al., 2007). High-resolution paleoclimate data for the whole course of hominin evolution would be very interesting but do not yet exist.

The models of gene–culture coevolution described above, which predate the high-resolution paleoclimate data, suggest that a cognitive capacity to support a costly system for cultural transmission and evolution is favored by just such high-amplitude millennial and submillenial scale variations as occurred during at least the last four glacial cycles. Without such variation, genes and nontransmitted phenotypic flexibility are sufficient to allow a population to adapt to variation (Boyd and Richerson, 1985, pp. 125–131; Wakano et al., 2004) without the need for the faster-tracking but expensive cultural system. The paleoclimate data, as they currently stand, are consistent with the hypothesis that the evolution of human culture has been in response to increasing environmental variation over time. We know that brain-size increase is not unique to humans. Many mammalian lineages show increased brain size in the last couple of million years (Jerison, 1973). Increases in mammalian brain size averaged over many lineages might be taken as a paleoclimate index of the amount of high-frequency environmental variation, on the grounds that costly nervous tissue would not evolve unless useful for adapting to high-frequency environmental change by individual learning and simpler forms of social learning (Aiello and Wheeler, 1995; Reader and Laland, 2002; Sol et al., 2005).

## CURRENT EVIDENCE AND PROBLEMS TO SOLVE

In this section, we outline the still-modest evidence that culture-led gene–culture coevolution has been the dominant mode of human evolution, perhaps reaching back to the divergence of hominins from our last common ancestor with the other apes. The modest culture of chimpanzees and many other organisms (Laland, 1999; Whiten, 2000; Rendell and Whitehead, 2001) might also induce important gene–culture coevolution by a cultural Baldwin effect.

The best evidence about gene–culture coevolution comes from the present and immediate past (Laland et al., 2010). Estimating the current strength and direction of selection is a classic topic in evolutionary biology (Endler, 1986), and social scientists have conducted similar studies (Hannan and Freeman, 1989; Hout et al., 2001). The environmental, genetic, and cultural data are rather good for the last 10 millennia. However, some of the most interesting questions come from deeper history, where all three kinds of investigations meet limits. Ancient ecosystems and their variation are hard to reconstruct (Huntley and Allen, 2003), evidence of distant past selection is less precise than for recent selection, and the number of fossils and artifacts discovered and their condition decline with time [e.g., Ungar et al. (2006)]. The hope is that evolutionary genomics and related functional studies will provide a powerful third source of data to complement paleoenvironmental and paleoanthropological data. The way forward will be to make optimal use of all three forms of data, each with inevitable limitations, in evaluating hypotheses about our evolution.

### Current Selection

Most but not all contemporary human populations have experienced rapid and dramatic cultural change in recent times due to economic development and the globalization of culture. Diseases and domesticates from all around the world have been introduced to climatically compatible regions. Large populations of mixed-race people have emerged. Many populations have reduced exposure to infectious diseases. Some populations have become so wealthy that consumption of food leads to diseases of nutritional excess rather than diseases of nutritional deficiency. In the past two centuries, beginning in Europe, an increasing number of societies have become highly urbanized. Kin have become less important in social networks in urban societies, leading to a host of fitness-related changes including demographic transitions and increasing tolerance for lifestyles that do not result in reproduction (Newson et al., 2007). Kin-dense social networks arguably support norms that encourage reproduction in a society because kin selection will have favored kin taking more interest in the reproduction of kin than in the reproduction of nonkin friends.

These changes all seem likely to generate measurable selection on genes. Some of these genetic changes are likely to result from relaxed selection, for example, due to the reduced importance of infectious disease and nutritional deficiency in many populations. Some are likely to result from positive selection for resistance to new environments. For example, modern urban environments are often hygienically cleaned, apparently leading to the IgE component of the immune system to respond to inappropriate targets such as one's own tissue or harmless pollens (Yang et al., 2007; Gould and Sutton, 2008). Some of these diseases, like asthma, have appreciable death rates among children and young adults. A number of genes that might be targets of selection are known to be involved in asthma.

Some of the complexities of gene–culture coevolution can be illustrated by the impact of the demographic transition on genetic and cultural evolution. Whereas most of us celebrate the modern steep drop in fertility from the point of view of moderating anthropogenic climate change and similar problems, the first-order effect of natural selection is to favor the efficient conversion of resources into offspring. Thus, we might expect to see current selection favoring more pronatalist behavior in postdemographic transition societies. On the genetic side, a study of the heritability of fertility in Danish twins showed that the heritability of fertility was negligible in predemographic transition times but has become appreciable in later cohorts (Kohler et al., 1999; Murphy and Knudsen, 2002). Formerly, pronatalist culture, which must have been the norm in most times and places throughout our evolutionary history, would have effectively encouraged most people to reproduce efficiently, despite minor genetic variation that might have led some people not to reproduce. A drastic fall in average fertility has likely caused variation that was once neutral, or nearly so, to have a much stronger effect on phenotypes. Two studies report that life-history characteristics are currently responding to selection (Kirk et al., 2001; Helle, 2008). Women seem to be under selection to enter menarche earlier, have earlier first births, and to reach menopause later. They seem to sacrifice height in the process of earlier reproduction. As to mechanism, earlier first births may simply result from earlier menarche, exposing more impulsive teenagers to risk of pregnancy.

Stearns and coauthors used the Framingham Heart Study to estimate the effects on lifetime reproductive success of traits measured in that study (Byars et al., 2010). Together with estimates of heritabilities of traits, they estimated selection strength on these traits. Women are under measurable selection for shorter but heavier bodies, earlier reproduction but also delayed menopause, as in the studies described just above, and lower blood pressure and lower cholesterol. The latter two traits suggest selection to adapt to the sedentary lifestyles and rich diets in the contemporary developed world.

Culture is also under selection to increase birth rates. Some subcultures, such as Old Order Anabaptists, have proven quite resistant to cultural modernization and have continued to reproduce at natural fertility levels (~7 children per woman). Anabaptist populations are apparently growing very rapidly (Hostetler, 1993; Kraybill and Bowman, 2001). Hout et al. (2001) estimated the selective effects of other religious beliefs. The main effect in the United States seems to be that religious people have about twice as many children as the unchurched; differences among many denominations are otherwise modest. At the global level, religion is currently spreading faster than secularism because religious people are having more children (Norris and Inglehart, 2004). Sociologists of religion have argued that early Christianity spread in part by demographic increase in the Roman Empire because of its pronatalist proscriptions and prescriptions (Stark, 1997).

**Selection in the Holocene**

About 11,500 years ago the climate stabilized, beginning the current relatively invariant, warm, and wet interglacial. Over the next few thousand years, most human populations adopted some form of agricultural subsistence (Richerson et al., 2001). Late Pleistocene humans appear to have depended disproportionately on game animals for subsistence (Stiner et al., 2000). Thus, switching to a diet rich in plant carbohydrates confronted people with dietary challenges (Cohen and Armelagos, 1984). Plant-rich diets also meant that human numbers could increase, leading to the acquisition of new epidemic diseases, often from domestic animals (Diamond, 1997). Dense populations also led to the cultural evolution of new forms of social organization to replace the smaller-scale egalitarian societies that typify many hunter-gathers. Large social systems arose with hierarchically organized authority and an elaborate division of labor.

The evidence suggests that many new genes came under selection in the Early and Middle Holocene (Hawks et al., 2007). Some of these are familiar human polymorphisms already discussed, such as the *HBB* sickle cell gene, the *G6PD* malaria protection gene, and the *LCT* adult lactose secretion gene. Other interesting genes include amylase copy-number polymorphisms. Populations with a recent history of diets rich in starch have more copies of the gene coding for amylase (Perry et al., 2007). The functional annotations of genes identified in large-scale scans [e.g., Sabeti et al. (2006)] flag many as potentially of significance in disease resistance or dietary adaptations. As the vast task of identifying the functions of many genes proceeds, we anticipate many similar cases to emerge (Bryk et al., 2008; Hughes et al., 2008; Ryan et al., 2008).

The category that will be controversial is genes related to behavior. The transformation of human social systems in the Holocene is every bit as dramatic as the transition in diet and disease exposure. Should we expect that many genes adapted to more complex and more hierarchical societies have arisen in the Holocene? Cochran and Harpending (2009) have suggested that the Ashkenazi Jews have high intelligence, and a concentration of genetic diseases with neurological symptoms, due to their Medieval specialization in the businesses of banking and long-distance trade, and later in various managerial occupations. These jobs, emphasizing intellectual skills, generated selection for high IQ. Jews of that time were also relatively genetically isolated. Some of these genes are perhaps overdominant, leading to neurological pathologies when homozygous. One might imagine that the human division of labor is extensively supported by genetic specializations favoring different occupations. As cultures developed a larger number of economic and social roles, human genetic diversity might have increased to diversify human capabilities and inclinations. The honeybee division of labor is supported by queens mating multiply and so diversifying the genes of workers, whose differing genotypes are better at different tasks (Mattila and Seeley, 2007). This hypothesis suggests that genes controlling such things as personality should be more variable in populations that have long had a history of an extensive division of labor.

On the other hand, culture is a tremendous force for generating behavioral variation independently of genetic variation. Thus, human genetic variation for behavioral traits may be large because cultural variation shelters much genetic variation from selection. Literacy rates in societies with good education systems can approach 100% despite the fact that reading is not something human brains evolved to do. Rather, cultures evolved writing systems that take advantage of parts of the brain evolved to do quite different things (Dehaene, 2009). Cultures find ways to finesse disabilities so that the blind and dyslexic can learn to read. The idea that traits with high heritabilities such as IQ are unaffected by the cultural environment is falsified by the rapid secular increase in IQ in many developed countries during the 20th century (Flynn, 2007), and by the fact that IQ is much less heritable among populations with lower socioeconomic status (Turkheimer et al., 2003). Likewise, IQ is correlated across countries with stage of modernization (Newson and Richerson, 2009). The amount and quality of education seem to explain most of the variation in IQ between groups and over time within groups (Nisbett, 2009). Botticini and Eckstein (2007) argue that a tradition of education and literacy accounts for Jews entering jobs requiring high intellectual skills. Of course, this hypothesis and Cochran and Harpending's are not mutually exclusive. *To what extent* are the genes that underlie behavioral variation in humans evolving mostly

by drift and mutation because they are protected from selection by culture, and *to what extent* have they been under frequency-dependent selection to support the division of labor in complex societies?

**Selection in the Plio-Pleistocene**

Humans emerged from the Late Pleistocene with a highly advanced capacity for culture and promptly evolved agricultural subsistence systems that radically altered human environments. The strong coevolutionary impact of cultural changes on genes in the Holocene is not surprising. But how far back into hominin history was this mode of coevolution important? Theory points to the speed of cultural evolution compared with genetic evolution. Even rudimentary culture capacities could support appreciable amounts of culture-driven gene–culture coevolution. This idea is difficult to test in humans given the limitations of the current record mentioned in the introduction to this section. Certain aspects of the record are now reasonably well understood, namely skeletons and stone tools. Genomic clocks can potentially be calibrated by matching the evolution of genes directly affecting skeletons and abilities to make stone tools to the paleoanthropological record. If genomic analysis can provide at least rough dates for when traits and capacities that are more poorly represented in the paleoanthropological record evolved, it will provide an important new source of information about how the coevolutionary process works. The logic of the argument can be illustrated by the refutation of an early coevolutionary hypothesis proposed by Sherwood Washburn (1959). Washburn speculated that a coevolutionary process was set up by the development of traditions of making simple stone tools. The use of tools created environments that favored the specialization of hands for toolmaking, leading toward upright posture. As hands became more specialized for toolmaking, selection would favor larger brains, including improved manual dexterity in fine manipulations, that would underpin more complex tool traditions. This hypothesis is not correct, at least not in the simple form that Washburn proposed. Australopithecines were bipedal for several million years without any evidence of brain-size increase or tool use. Many plausible scenarios about human evolution in the Plio-Pleistocene have been advanced. Most of these are hard to test using skeletal and stone tool evidence alone. We illustrate how genomic data might help improve our understanding of hominin evolution in the Plio-Pleistocene.

We first sketch the Plio-Pleistocene evolutionary events known from skeletons and artifacts and then conjecture about how genomic data might help resolve issues by the paleoanthropology of this period. Then we turn to the problems of the evolution of language and social organization.

Events in the evolution of these two especially important features of gene–culture coevolution have been difficult to reconstruct because the skeletal and artifact data regarding them are so enigmatic. Here genomic data are likely to prove especially useful. The genome-wide scans for genes under selection in the last few tens of thousands of years described in the main text are based on single nucleotide polymorphisms (SNPs) from a relatively limited sample of genomes. These data provide only a relatively low-resolution picture of genetic variation. The 1000 Genomes Project is in the process of fully sequencing at least 1,000 genomes from 11 populations representing the major regions of the world (http://www.1000genomes.org/page.php). The cost of such full sequences will probably continue to fall. Over the next decade, a large representative sample of high-resolution sequences should be available. We can anticipate that the information in these sequences, together with advances in functional genomics, will offer great insights into the deep evolutionary history of our lineage.

**Selection in the Late Pleistocene**

To judge from paleoanthropological data, the period from ~250 kya to 50 kya was the time interval over which people became behaviorally modern. African populations had rather modern, but not completely modern, skeletons and large brains early in this period (Rightmire, 2009b), but mostly made comparatively simple stone tools until about 40 kya. About this time, anatomically modern Africans dispersed from Africa to Eurasia. In western Eurasia and northern Africa, anatomically modern populations began making sophisticated Upper Paleolithic stone tools and art objects about 40 kya. Ephemeral episodes of more sophisticated tool making do occur much earlier in Africa (Jacobs et al., 2008). The early, if ephemeral, occurrence of sophisticated stone tools at the same time period as large-brained early modern humans is consistent with behavioral modernization being toward the beginning of this period. If so, the fact that anatomically modern humans were confined for so long to Africa, usually making fairly simple stone tools, is puzzling. If people were capable of modern behavior, why did they so seldom exhibit it? Why was their dispersal out of Africa so late? Klein (2009) suggests that a fortuitous mutation perhaps ~60 kya led to the final modernization of humans and to our movement out of Africa. An uptick in the millennial- and submillenial-scale climate variation after about 70 kya might have advantaged the more cultural hominins and led to a substantial bout of gene–culture coevolution. Or perhaps the explanation is entirely environmental and genes played little or no role. Simply increasing human population densities in some times and places could support the evolution of more complex technology (Henrich, 2004b; Powell et al., 2009).

As mentioned in the earlier, genomic studies have already revolutionized our understanding of our migration out of Africa, following the pioneering mitochondrial DNA phylogeny of Cann, Stoneking, and Wilson (1987). By now it is clear that much of the genetic variation and genetic diversity in human populations is consistent with a spread out of Africa about 60–50 kya (Ramachandran et al., 2005; Liu et al., 2006). Examples of genes that very likely came under selection in this period include genes affecting skin pigmentation (McEvoy et al., 2006; Myles et al., 2007). As with genes selected in the Holocene, different populations have reached parallel solutions to the same adaptive problem. The genes that underlie the light skin adaptation to increase vitamin D photosynthesis in cold, low-sunlight environments are different in eastern and western Eurasia (Jablonski and Chaplin, Chapter 9, this volume).

Ideally, genomic data will provide an accurate timescale for major evolutionary events, which can then be used in conjunction with paleoanthropological data to resolve some of the puzzles noted above. This quest for well-dated selection events will require more data and improved methods. The best tool for younger events, dates estimated from the long haplotypes associated with genes under selection, is nearly erased by recombination in this earlier period. The reduced diversity and excess of rare haplotypes in the regions flanking genes under selection in theory will lead to datable genomic events in this time period (Sabeti et al., 2006). An interesting example of another kind of data that might prove useful is the study of the evolution of human commensals and parasites. For example, the human body louse lives in clothing but feeds on the body. It evolved from the head louse, which lives in hair, 72 kya ± 42 kya (Kittler et al., 2003). Thus, clothing must have evolved fairly recently, perhaps associated with the out-of-Africa migration of anatomically modern humans to higher latitudes. Aside from the human genome itself, we wonder how much evolutionary history might be reconstructed from the diverse microflora that inhabit our digestive tract and skin (Hattori and Taylor, 2009).

Complete sequences of Neandertal autosomal DNA promise to revolutionize our understanding of selection in the Late Pleistocene (Green et al., 2006). Improvements in the database of fossil mitochondrial DNA sequences also promise much (Krause et al., 2010). Assuming that the ancestral *Homo heidelbergensis* population that gave rise to Neandertals and ourselves lived around 200–600 kya (Weaver et al., 2008), and if there was no introgression of genes from Neandertals to anatomically modern humans (or that such introgression as did occur is detectable), then any genetic variants that we share with Neandertals (such as, possibly, the derived *FOXP2* variant) must have had its origin before the date of separation of the two species. Derived genes not shared with Neandertals are candidates to have evolved on the anatomically modern lineage. We might

not want to discount the possibility of convergent evolution in the two species. Neandertals had brains as large as anatomically modern humans (Klein, 2009). By some accounts, Neandertals proved as capable of sophisticated culture as anatomical moderns. Just before we came into contact with them, and after the uptick in millennial- and submillennial-scale variation ~60 kya, Neandertals may have independently evolved the modern behaviors ascribed to the makers of the Upper Paleolithic industries of western Eurasian anatomical moderns (d'Errico, 2003; Zilhão et al., 2010). Introgression between anatomically modern humans and Neandertals is a possibility (Cochran and Harpending, 2009), and what genes did introgress would be informative if they can be reliably detected, particularly if they generated parallel selective sweeps in the two species.

For this period, we have nothing like the unmistakable signature of cultural changes driving genetic changes that we see in the Holocene. If anything, genetically determined traits such as brain size seem to appear in the paleoanthropological record preceding, rather than following, the most conspicuous cultural changes. Perhaps the most interesting single question here is whether genes underlying modern behavior evolved early or late in this period. The durable artifacts tend to support a late interpretation, because a great number of traits that are most diagnostic of modern behavior, such as symbolic behaviors (art), develop rather late. If Neandertals did independently evolve modern behavior, then perhaps parallel or convergent genetic or cultural responses to increased climate variation can explain the pattern. The capacity for modern behavior need not necessarily have been present in the last common ancestor. The skeletons of early anatomically modern humans are still very robust and nonmodern in other ways (Rightmire, 2009b). The fossils and stone tools do not necessarily contradict the hypothesis that large-brained but archaic anatomical modern genes were coevolving in response to Middle Paleolithic cultural innovations. The combination of large brains and comparatively simple technology is a major puzzle nonetheless. How were our ancestors supporting such an energetically expensive organ unless by modern or near-modern behavior? Even the anatomically modern humans that left Africa and moved eastward to eastern Eurasia and Australia did so using relatively simple Middle Paleolithic toolkits (Foley and Lahr, 1997). The most dramatically modern Upper Paleolithic industries rich in symbolic artifacts were seemingly confined to western Eurasia and northern Africa for tens of thousands of years after 40 kya.

The especially intense pattern of millennial- and submillennial-scale variation after 70 kya suggests that environmental conditions potentially played some role. We might imagine that the adaptive advantages of Middle Paleolithic stone tool traditions were sufficient to induce the evolution of very large brains in both anatomical moderns and Neandertals.

Perhaps the achievement of ephemeral sophisticated industries in Africa before 70 kya, and later more permanently in western Eurasia, depended upon larger populations, leading to the ability to accumulate more innovations. Rather than a bottleneck around 70 kya as mitochondrial coalescence data suggest, perhaps human populations were chronically rare before 70,000 kya. Imagine that humans were competing in a rather crowded guild of top carnivore species: lions, leopards, cheetahs, and other large cats; hyenas; wild dogs; wolves; and bears. More variable environments, to which humans could adapt culturally, might have given our species a competitive advantage. An increase in millennial- and submillennial-scale climate variation might thus have led to the spread of moderns out of Africa, and to population densities high enough to lead to Upper Paleolithic and similar industries (Richerson et al., 2009).

**Selection from the Late Pliocene to Middle Pleistocene**

Events deeper in the evolution of hominins are naturally even more opaque. The interesting high-frequency part of the paleoclimate record is seriously deficient for this period. During the long period from about 2.6 to 1 million years ago, when the low-resolution record was dominated by the 41,000-year cycle, early members of our own genus *Homo* enter the fossil record, particularly *H. erectus* sensu lato. These populations had relatively modern postcrania and brain sizes relative to body sizes intermediate between Australopithecines (and living apes) and anatomically modern humans and Neandertals (Ruff et al., 1997). Many, if not most, of the major genetic changes between humans and the rest of the apes probably occurred in this period, during the transitions from Australopithecines to *H. habilis* and from *H. habilis* to *H. erectus.* According to some interpretations, *H. erectus* had a rather modern physique and an enlarged brain relative to body size (McHenry and Coffing, 2000). Subsistence activities might have included a considerable ability to acquire meat and fat from hunting. For example, an important component of human hunting is the ability to run down large- and medium-sized game. Humans from *H. erectus* onward could probably run efficiently and sweat to keep our body temperature down during extended exercise. *H. erectus* hunters could thus probably have run medium-sized herbivore prey until they were exhausted or overheated or both, and then dispatched them with unsophisticated weapons (Bramble and Lieberman, 2004; Liebenberg, 2006; Jablonski and Chaplin, Chapter 9, this volume). We can expect to find genes related to a large variety of specifically human traits to have evolved in this period, but in most cases we will have to entertain the hypotheses that they evolved earlier in Australopithecines or in post-*H. erectus* hominins.

Early *Homo* skeletal material is loosely associated with two successive tool traditions, the Oldowan and the Acheulean. *H. erectus* spread out of Africa and into island southeast Asia, tolerating temperate climates and apparently crossing deep water, apparently some 1.7 mya (Rightmire et al., 2006). Some authorities emphasize the expedient simplicity of the Oldowan and early Acheulean industries. De la Torre and colleagues (2003, 2008) argue that a rather sophisticated appreciation of the properties of stone, and a fairly sophisticated approach to knapping, characterized these two industries. Sharon (2009) presents evidence that Acheulean makers of large biface tools had efficient and culturally variable techniques for producing these signature artifacts. A recently published Acheulean campsite dating to 750 kya seems to have been fairly complex. It contained remains suggesting that *H. erectus* could exploit a wide variety of plant and animal resources, including fish and acorns, and that they controlled fire (Alperson-Afil et al., 2009). Evidence for still-earlier use of fire is controversial (Wrangham, 2009). Interestingly, reports on living individuals with primary microcephaly (small brains but without organizational disruptions) indicate that they suffer only mild to moderate mental retardation (Cox et al., 2006). Perhaps these brains are a clue to the cognitive capabilities of *H. erectus*. *H. erectus*'s brain architecture and behavior might have been rather modern in many respects. Donald (1991) suggests that *H. erectus* had advanced abilities to imitate motor patterns but still lacked speech. He reviews 19th-century data on deaf mutes as evidence that alinguistic people would be capable of imitating many if not most modern skills except ones directly dependent on language. Thus, culture-led gene–culture coevolution could have been an active process in this period. After 1 mya, the 100-ky cycle came to dominate the low-frequency component of the climate record. Early in this period, larger-brained hominins, often lumped into the taxon *H. heidelbergensis*, evolved in Africa and western Eurasia (Rightmire, 2009a). Thus, there are hints, but at this point only bare hints, that changes in climate variation were increasing selection in favor of more sophisticated culture capacities. Some progress has been made on the representation of tool use in the brain (Peeters et al., 2009). Many genes associated with the ability to make and use tools probably evolved during this long period.

Since the sequencing of the chimpanzee genome, a considerable amount of effort has gone into searching for the differences between the two species (Kehrer-Sawatzki and Cooper, 2007; Portin, 2007, 2008; Varki and Nelson, 2007). Many candidates for genes that have come under selection have turned up in these comparisons. Some of the apparently most interesting genes, such as copy number in the gene MGC8902, have unknown function. The large OR family of genes (~1,000–1,400 loci) involved in odor perception has a very high percentage of nonfunctional

genes in humans, although some specific genes seem to have undergone positive selection.

This pattern of loss of function of olfactory genes is related to the reduced area of olfactory epithelium and relatively small olfactory bulb in humans. Likely enough, the development of cooking and the use of cultural traditions to identify suitable food items reduced our dependence on olfaction. The beginning of cooking likely also caused major changes in human diets which should be reflected in the genome (Wrangham, 2009). Our Australopithecine ancestors were probably largely herbivorous. Early species of *Homo* were probably generalist omnivores with significant access to hunted and scavenged fat and meat (Ungar et al., 2006). By Middle and Upper Paleolithic times, stable isotope analysis and zooarchaeological remains suggest that humans were highly carnivorous (Stiner, 1992; Richards et al., 2001). The expansion of brains in *Homo* was very likely tied to improved nutrition via hunting and cooking (Leonard et al., 2007). Genes associated with dietary changes and brain-size increase should be correlated to each other and to patterns derived from paleoanthropology.

## Evolution of Language and Social Organization

Language and social organization were probably closely related in the course of human evolution. Much of our use of language is related to social life, and it is reasonable to assume considerable parallelism in their evolution (Dunbar, 1996). They are both features that fossilize poorly. Inferences about their presence or absence are not easy to make. For example, Philip Lieberman (2007) has long argued from anatomical evidence regarding the shape of the vocal tract that the capacity to clearly articulate modern vowel systems only emerged around 50 kya. He nevertheless thinks that ancient species of *Homo* had some useful capacity for speech. Indeed, there is perhaps a consensus among evolutionists writing on language that it evolved by culture-led gene–culture coevolution over an extended portion of our evolutionary history (Richerson and Boyd, in press). Nevertheless, dissenters on this point certainly exist. For example, Tattersall (2007) argues that articulate language must have originated only 50 kya. He cites not only the anatomical evidence but also the late first finds of unambiguous symbolic artifacts such as art. Those who imagine that language arose by prolonged culture-led coevolution differ greatly in the details of their scenarios. For example, Pinker (2003) argues that coevolution will lead to complex innate cognitive specializations for language. Kirby et al. (2007) use simulations to illustrate how the basic features of language might be cultural adaptations to preexisting cognitive constraints on language learning. That is, language evolved to fit our brain,

rather than the other way around (Deacon, 1997). If cultural adaptation is sufficiently powerful, it might lead to little or no coevolutionary pressure on innate cognitive mechanisms. Tomasello (2008) argues that language is a cultural construct and that most of the coevolved innate predispositions for language are shared with other cultural features. Although the involvement of the *FOXP2* gene in language evolution has turned out to be complex and controversial, the intense interest it has generated illustrates the questions we hope to answer with the help of genomic methods: What genes changed, when did they change, and what is the functional significance of the changes?

Many scenarios have been advanced in discussions of the evolution of social organization, although it has not received the same amount of attention as language. Lovejoy (2009) argues that reduced canines in the possible ancestral hominin *Ardipithecus ramidus* indicate that this early species already exhibited reduced intrasexual antagonism and greater social adhesion on the part of both males and females. Hrdy (2009) reviews a large body of evidence regarding the role of cooperative breeding (assistance to females with dependent offspring by others), concluding that cooperative breeding must have evolved in the hominin lineage before brain enlargement. The costly big brains and long juvenile periods of great apes already strain the ability of mothers to rear such offspring. Despite having highly dependent infants needing to grow even larger brains, human interbirth intervals are shorter than those of great apes, something only possible with alloparental assistance. Burkart et al. (2009) argue that cooperative breeding would have laid the initial basis for cooperative psychological predispositions in humans. Interesting progress has been made on the possible role of a vasopressin receptor gene polymorphism in human bonding (Walum et al., 2008). The comparative biology of human reproduction suggests that humans experience relatively low sperm competition, an indication of male investment in provisioning offspring rather than competing for mates (Anderson et al., 2005; Martin, 2007). Derived alleles for genes expressed in testes and sperm turn up in scans for evidence of selective differences between humans and chimpanzees (Nielsen et al., 2005).

However, much genetic change also appears to have happened in the Late Pleistocene and even in the Holocene according to data we have reviewed in this chapter. Perhaps important innovations involving social predispositions occurred as late as 50 kya (Klein, 2009) or even in the Holocene (Cochran and Harpending, 2009). Once again, the evidence for just how far back in time the culture-led mode of gene–culture coevolution can be pushed is an open question to which evolutionary genomics will have much to contribute. As with language, not only is timing of important events uncertain but also the division of labor between genes and culture. We (Richerson and Boyd, 1998, 1999) have suggested that humans' social

psychology was fairly extensively remodeled by gene–culture coevolution. However, in ethnographically known societies, culturally transmitted norms and institutions do much heavy lifting. We do not anticipate finding that dramatic genetic changes were necessary to accompany the evolution of social complexity in the Holocene. The simpler societies known ethnographically rely heavily on norms and institutions to regulate social life, so no revolution in our innate psychology seems necessary to account for complex societies. Cosmides et al. (Chapter 15, this volume) suggest that much more of the load is carried by content-rich cognitive adaptations than by transmitted culture. Functional and developmental genomics should eventually lay a foundation for understanding the roles of genes and culture in current behavior and in the past evolution of current behavioral capacities.

## CONCLUSIONS

Genomics has already made quite substantial contributions to our understanding of human evolution, beginning with the use of mitochondrial DNA variation to understand the timing of events in recent human evolution and to provide a window into human paleodemography, including past population sizes and migration patterns. The use of linkage disequilibrium to identify genes under recent selection suggests a massive Holocene wave of genetic change initiated by the cultural evolution of agricultural subsistence. Even here, our lack of knowledge of the functional significance of most of the alleles that have been under selection hides most of the details from us. As regards Plio-Pleistocene gene–culture coevolution, we are still at the very beginning of an understanding. In addition to a poor understanding of gene function, it is not clear how much information gene sequences contain about the timing of their selective history. Tools besides simple linkage disequilibrium suitable for deeper time will be required if genomics is to make a major contribution to resolving the many puzzles of the paleoanthropological record. We expect continued rapid progress.

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# 13

# The Cognitive Niche: Coevolution of Intelligence, Sociality, and Language

STEVEN PINKER

Although Darwin insisted that human intelligence could be fully explained by the theory of evolution, the codiscoverer of natural selection, Alfred Russel Wallace, claimed that abstract intelligence was of no use to ancestral humans and could only be explained by intelligent design. Wallace's apparent paradox can be dissolved with two hypotheses about human cognition. One is that intelligence is an adaptation to a knowledge-using, socially interdependent lifestyle, the "cognitive niche." This embraces the ability to overcome the evolutionary fixed defenses of plants and animals by applications of reasoning, including weapons, traps, coordinated driving of game, and detoxification of plants. Such reasoning exploits intuitive theories about different aspects of the world, such as objects, forces, paths, places, states, substances, and other people's beliefs and desires. The theory explains many zoologically unusual traits in *Homo sapiens*, including our complex toolkit, wide range of habitats and diets, extended childhoods and long lives, hypersociality, complex mating, division into cultures, and language (which multiplies the benefit of knowledge because know-how is useful not only for its practical benefits but as a trade good with others, enhancing the evolution of cooperation). The second hypothesis is that humans possess an ability of *metaphorical abstraction*, which allows them to co-opt faculties that originally evolved for physical problem solving and social coordination, apply them to abstract

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subject matter, and combine them productively. These abilities can help explain the emergence of abstract cognition without supernatural or exotic evolutionary forces and are in principle testable by analyses of statistical signs of selection in the human genome.

The bicentennial of Darwin's birth and sesquicentennial of the publication of the *Origin of Species* have focused the world's attention on the breathtaking scope of the theory of natural selection, not least its application to the human mind. "Psychology will be based on a new foundation," Darwin famously wrote at the end of the *Origin*, "that of the necessary acquirement of each mental power and capacity by gradation. Light will be thrown on the origin of man and his history."

Far less attention has been given to the codiscoverer of natural selection, Alfred Russel Wallace, despite his prodigious scientific genius, and it is unlikely that the bicentennial of his birth in 1823 will generate the same hoopla. One reason was that Wallace turned out to be less prescient about the power of natural selection as an explanation of adaptive complexity in the living world. In particular, Wallace notoriously claimed that the theory of evolution by natural selection was inadequate to explain human intelligence:

> Our law, our government, and our science continually require us to reason through a variety of complicated phenomena to the expected result. Even our games, such as chess, compel us to exercise all these faculties in a remarkable degree. . . . A brain slightly larger than that of the gorilla would . . . fully have sufficed for the limited mental development of the savage; and we must therefore admit that the large brain he actually possesses could never have been solely developed by any of those laws of evolution, whose essence is, that they lead to a degree of organization exactly proportionate to the wants of each species, never beyond those wants. . . .
>
> Natural selection could only have endowed savage man with a brain a few degrees superior to that of an ape, whereas he actually possesses one very little inferior to that of a philosopher.
>
> Wallace (1870b, pp. 340, 343)

The upshot, claimed Wallace, was that "a superior intelligence has guided the development of man in a definite direction, and for a special purpose" (1870b, p. 359).

Few scientists today accept Wallace's creationism, teleology, or spiritualism. Nonetheless it is appropriate to engage the profound puzzle he raised; namely, why do humans have the ability to pursue abstract intel-

lectual feats such as science, mathematics, philosophy, and law, given that opportunities to exercise these talents did not exist in the foraging lifestyle in which humans evolved and would not have parlayed themselves into advantages in survival and reproduction even if they did?

I suggest that the puzzle can be resolved with two hypotheses. The first is that humans evolved to fill the "cognitive niche," a mode of survival characterized by manipulating the environment through causal reasoning and social cooperation. The second is that the psychological faculties that evolved to prosper in the cognitive niche can be coopted to abstract domains by processes of metaphorical abstraction and productive combination, both vividly manifested in human language.

## THE COGNITIVE NICHE

The term cognitive niche was proposed by Tooby and DeVore (1987) to explain the constellation of zoologically unusual features of modern *Homo sapiens* without resorting to exotic evolutionary mechanisms.

Their account begins with the biological commonplace that organisms evolve at one another's expense. With the exception of fruit, virtually every food source of one animal is a body part of some other organism, which would just as soon keep that body part for itself. As a result, organisms evolve defenses against being eaten. Animals evolve speed, stealth, armor, and defensive maneuvers. Plants cannot defend themselves with their behavior, so they resort to chemical warfare, and have evolved a pharmacopeia of poisons, irritants, and bitter-tasting substances to deter herbivores with designs on their flesh. In response, eaters evolve measures to penetrate these defenses, such as offensive weapons, even greater speed or stealth, and organs such as the liver that detoxify plant poisons. This in turn selects for better defenses, selecting for better offenses, and so on, in a coevolutionary arms race, escalating over many generations of natural selection.

Tooby and DeVore (1987) suggest that humans exploit a cognitive niche in the world's ecosystems. In biology, a "niche" is sometimes defined as "the role an organism occupies in an ecosystem." The cognitive niche is a loose extension of this concept, based on the idea that in any ecosystem, the possibility exists for an organism to overtake other organisms' fixed defenses by cause-and-effect reasoning and cooperative action—to deploy information and inference, rather than particular features of physics and chemistry, to extract resources from other organisms in opposition to their adaptations to protect those resources. These inferences are played out internally in mental models of the world, governed by intuitive conceptions of physics, biology, and psychology, including the psychology of animals. It allows humans to invent tools, traps, and weapons, to extract

poisons and drugs from other animals and plants, and to engage in coordinated action, for example, fanning out over a landscape to drive and concentrate game, in effect functioning like a huge superorganism. These cognitive stratagems are devised on the fly in endless combination suitable to the local ecology. They arise by mental design and are deployed, tested, and fine-tuned by feedback in the lifetimes of individuals, rather than arising by random mutation and being tuned over generations by the slow feedback of differential survival and reproduction. Because humans develop offenses in real time that other organisms can defend themselves against only in evolutionary time, humans have a tremendous advantage in evolutionary arms races. Even before the current anthropogenic mass extinction, prehistoric humans are believed to have caused significant extinctions of large fauna whenever they first entered an ecosystem.

The theory of the cognitive niche helps explain many zoologically unusual features of *H. sapiens*: traits that are universal across human cultures (Brown, 1991) but are either unique or hyperdeveloped (especially in combination) with respect to the rest of the animal kingdom. Three in particular make our species stand out.

### Technological Know-How

Humans use and depend upon many kinds of tools, which involve multiple parts and complicated methods of fabrication. The tools are deployed in extended sequences of behavior and are acquired both by individual discovery and learning from others. They are deployed to capture and kill animals, to process foods (including cooking, fermenting, soaking, peeling, and crushing them to remove toxins and increase the availability of nutrients), and to generate and administer medicinal drugs (Kingdon, 1993; Wrangham, 2009, p. v). This reasoning is supported by "intuitive theories"—folk understandings of physics (in particular, objects, substances, and the forces that impinge on them), geometry (places, paths, and directions), biology (essences that give organisms their form and propel their growth, motion, and physiological processes), and psychology (internal, immaterial beliefs and desires) (Spelke et al., 1992; Leslie, 1994; Pinker, 1997, 2007; Carey, 2009).

### Cooperation Among Nonkin

Humans cooperate with other humans: they trade goods, favors, know-how, and loyalty, and act collectively in childrearing, gathering, hunting, and defense. This cooperation extends to other humans who are not related to them, in shifting partnerships, coalitions, and trading

relationships, and thus must be explained not by kin selection but by mutualism or reciprocity (Trivers, 1971).

The evolution of cooperation by reciprocal altruism requires a number of cognitive adaptations, which in fact appear to be well-developed in humans (Trivers, 1971). They include the recognition of individuals (Kanwisher and Moscovitch, 2000); episodic memory for their actions (Klein et al., 2002); an ability to classify those actions in terms of whether they violate a reciprocity contract (Cosmides and Tooby, 1992; Cosmides et al., Chapter 15, this volume); a suite of moral emotions such as sympathy, gratitude, anger, guilt, and trust, which impel an individual to initiate cooperation, reward reciprocators, and punish cheaters (Trivers, 1971; Haidt, 2002); and the drives to ascertain the competence, integrity, and generosity of others (through gossip and other forms of due diligence) and to burnish one's own reputation for these traits (Ridley, 1997; Nowak and Sigmund, 1998).

Because humans cooperate by at least three different kinds of relationship, governed by incompatible rules for the distribution of resources—reciprocal altruism, mutualistic sharing, deferring to dominant individuals—dyads can dynamically switch among kinds of relationship according to their history, kinship, social support, the resource at stake, and the context (Fiske, 1991). The demands of this negotiation account for many of the complex aspects of human social life such as politeness, hypocrisy, ritual, and taboo (Pinker et al., 2008; Lee and Pinker, 2010).

### Grammatical Language

Although many animals communicate, humans appear to be unique in using an open-ended combinatorial system, grammatical language. In grammatical language, signals (words) are arbitrarily paired with concepts, and can be rearranged in novel hierarchical configurations (phrases embedded within phrases) in such a way that the meaning of the sequence can be computed from the meanings of the individual symbols and the way that they are arranged (Chomsky, 1972; Pinker, 1991; Jackendoff, 2002). The semantic meanings of the symbols (nouns, verbs, prepositions, tense markers, and so on) are related to the basic cognitive categories that define intuitive theories: objects, substances, motion, causation, agency, space, time (Jackendoff, 1990; Pinker, 2007). The syntactic arrangements serve to express relationships among these concepts such as who did what to whom, what is where, and what is true of what (Pinker, 2007). Although every language must be learned, humans have an ability to coin, pool, and learn new words and rules and thus are not dependent on some other species as teachers (as is the case with apes), or even on a

longstanding linguistic community, to develop and use language (Senghas et al., 2004).

Grammatical language has clear advantages in the transmission of information. Because it allows messages to be composed out of elements, rather than drawn from a finite repertoire, it confers the ability to express an unlimited number of novel messages (Pinker, 1999; Nowak et al., 2000). Journalists say that when a dog bites a man, that is not news, but when a man bites a dog, that *is* news: the power of grammar is that it allows us to convey news, by arranging familiar words in novel combinations. Like other digital combinatorial systems in biology (RNA, DNA, proteins), language can generate vast numbers of structured combinations. The number of possible sentences (each corresponding to a distinct message) is proportional to the number of words that may appear in a position in a sentence raised to the power of the length of the sentence. With an approximate geometric mean of 10 choices available at every position in a sentence, one can estimate that a typical English speaker can easily produce or comprehend at least $10^{20}$ distinct sentences (Miller and Selfridge, 1950). This in turn makes it possible for language users to share an unlimited number of messages concerning specific events (who did what to whom, when, where, and why), generalized expertise (to accomplish this, do that), and flexible social contracts (if you do this, I'll do that).

Anyone who is skeptical that sophisticated reasoning, collaboration, and communication can bring survival advantages in a prehistoric lifestyle need only read ethnographic accounts of hunting or gathering in contemporary foraging peoples. One of many examples of hunter-gatherer ingenuity can be found in this description from the anthropologist Napoleon Chagnon of how the Yanomamö hunt armadillo:

> Armadillos live several feet underground in burrows that can run for many yards and have several entries. When the Yanomamö find an active burrow, as determined by the presence around the entry of a cloud of insects found nowhere else, they set about smoking out the armadillo. The best fuel for this purpose is a crusty material from old termite nests, which burns slowly and produces an intense heat and much heavy smoke. A pile of this material is ignited at the entry of the burrow, and the smoke is fanned inside. The other entries are soon detected by the smoke rising from them, and they are sealed with dirt. The men then spread out on hands and knees, holding their ears to the ground to listen for armadillo movements in the burrow. When they hear something, they dig there until they hit the burrow and, with luck, the animal. They might have to try several times, and it is hard work—they have to dig down 2 feet or more. On one occasion, after the hunters had dug several holes, all unsuccessful . . . one of them ripped down a large vine, tied a knot in

> the end of it, and put the knotted end into the entrance. Twirling the vine between his hands, he slowly pushed it into the hole as far as it would go. As his companions put their ears to the ground, he twirled the vine, causing the knot to make a noise, and the spot was marked. He broke off the vine at the burrow entrance, pulled out the piece in the hole, and laid it on the ground along the axis of the burrow. The others dug down at the place where they had heard the knot and found the armadillo on their first attempt, asphyxiated from the smoke.
>
> Chagnon (1992, pp. 78–79)

This jackpot was a reward for extraordinary feats of folk reasoning in taxonomy, physiology, physics, and geometry, some passed down from earlier generations, some improvised on the spot. And it depended on cooperative behavior among many individuals, coordinated by language.

**Other Extreme Human Traits**

Other zoologically unusual features of *H. sapiens* may be explained by the theory of the cognitive niche. The vast range of habitats and foods exploited by our species may in part have been facilitated by natural selection of the genes in local populations to ambient conditions such as solar radiation, diet, and disease (Bryc et al., Chapter 8, this volume; Hancock et al., Chapter 4, this volume; Jablonski and Chaplin, Chapter 9, this volume; Scheinfeldt et al., Chapter 5, this volume). But these local adaptations pale in comparison with those made possible by human technology. The Inuit's colonization of high latitudes may have been facilitated by adaptive changes in body shape and skin pigmentation, but it depended much more on parkas, kayaks, mukluks, igloos, and harpoons. This underscores that the cognitive niche differs from many examples of niches discussed in biology in being defined not as a particular envelope of environmental variables (temperature, altitude, habitat type, and so on), nor as a particular combination of other organisms, but rather the opportunity that any environment provides for exploitation via internal modeling of its causal contingencies.

Our extended childhoods may serve as an apprenticeship in a species that lives by its wits, and our long lives may reflect a tilt in the tradeoff between reproduction and somatic maintenance toward the latter so as to maximize the returns on the investment during childhood. The dependence of children's readiness for adulthood on their mastery of local culture and know-how may also shift the balance in male parental investment decisions between caring for existing offspring and seeking new mating opportunities. This in turn may have led to biparental care, long-term pair bonding, complex sexuality (such as female sexuality being unlinked from

fertility, and sexual relationships subject to variation and negotiation), and multigeneration parental investment (Hawkes, Chapter 11, this volume). Support for these hypotheses comes from the data of Kaplan (Kaplan and Robson, 2002), who has shown that among hunter-gatherers, prolonged childhood cannot pay off without long life spans. The men do not produce as many calories as they consume until age 18; their output then peaks at 32, plateaus through 45, then gently declines until 65. This shows that hunting is a knowledge-dependent skill, invested in during a long childhood and paid out over a long life.

Finally, the division of humankind into cultures differing in language, customs, mores, diets, and so on, is a consequence of humans' dependence on learned information (words, recipes, tool styles, survival techniques, cooperative agreements, and customs) and their peripatetic natures. As splinter groups lose touch with their progenitors over time, the know-how and customs that the two groups accumulate will diverge from one another (Richerson et al., Chapter 12, this volume).

## Hominid Evolution and the Cognitive Niche

Given that the opportunity to exploit environments by technology and cooperation are independent of particular ecosystems, why was it Pliocene hominids that entered (or, more accurately, constructed) the cognitive niche and evolved sophisticated cognition, language, and sociality, rather than a population from some other taxon or epoch? This kind of historical question is difficult, perhaps impossible, to answer precisely because the unusualness of *H. sapiens* precludes statistical tests of correlations between the relevant traits and environments across species. But if we consider the cognitive niche as a suite of mutually reinforcing selection pressures, each of which exists individually in weaker form for other species, we can test whether variation in intelligence within a smaller range, together with a consideration of the traits that were likely possessed by extinct human ancestors, supports particular conjectures.

Obviously any orthogenetic theory (such as Wallace's) stipulating that the emergence of our species was the goal of the evolutionary process is inconsistent with the known mechanisms of evolution. It is also apparent that intelligence, which depends on a large brain, is not a free good in evolution (Wallace, Chapter 7, this volume). Its costs include the metabolic demands of expensive neural tissue, compromises in the anatomy of the female pelvis necessary for bearing a large-headed offspring, and the risks of harm from birth, falls, and the mutation and parasite load carried by such a complex organ. The proper framing of the question must ask which circumstances made the benefits of intelligence outweigh the costs. The hypothesis is that the hominid ancestors, more so than any other species,

had a collection of traits that had tilted the payoffs toward further investment in intelligence.

One enabling factor may have been the possession of prehensile hands (an adaptation to arboreality) in combination with bipedality (presumably an adaptation to locomotion). We know from the fossil record that both preceded the expansion of the brain and the development of tool use (Wood, Chapter 1, this volume). Perhaps the availability of precision manipulators meant that any enhanced ability to imagine how one might alter the environment could be parlayed into the manufacture and carrying of tools.

A second contributor to the evolution of intelligence among hominid ancestors may have been an opportunistic diet that included meat and other hard-to-obtain sources of protein (Wrangham, 2009, p. v). Meat is not only a concentrated source of nutrients for a hungry brain but may have selected in turn for greater intelligence, because it requires more cleverness to outwit an animal than to outwit fruit or leaves.

A third may have been group living, again with the possibility of positive feedback: groups allow acquired skills to be shared but also select for the social intelligence needed to prosper from cooperation without being exploited.

Indirect support for the hypothesis that sociality and carnivory contributed to the evolution of human intelligence comes from comparative studies showing that greater intelligence across animal species is correlated with brain size, carnivory, group size, and extended childhoods and life spans (Boyd and Silk, 2006; Lee, 2007). I am unaware of any review that has looked for a correlation between possession of prehensile appendages and intelligence, although it is tantalizing to learn that octopuses are highly intelligent (Mather, 1995).

## Coevolution of Cognition, Language, and Sociality

Many biologists argue that a niche is something that is *constructed*, rather than simply entered, by an organism (Lewontin, 1984; Odling-Smee et al., 2003). An organism's behavior alters its physical surroundings, which affects the selection pressures, in turn selecting for additional adaptations to exploit that altered environment, and so on. A classic example is the way beavers generated an aquatic niche and evolved additional adaptations to thrive in it. The particulars of a *cognitive* niche are similarly constructed, in the sense that initial increments in cooperation, communication, or know-how altered the social environment, and hence the selection pressures, for ancestral hominids. It is surely no coincidence that the psychological abilities underlying technological know-how, open-ended communication, and cooperation among nonkin are all hyperdeveloped in

the same species; each enhances the value of the other two. (A similar feedback loop may connect intelligence with the life-history and behavioral-ecology variables mentioned in the preceding section.)

An obvious interdependency connects language and know-how. The end product of learning survival skills is information stored in one's brain. Language is a means of transmitting that information to another brain. The ability to share information via language leverages the value of acquiring new knowledge and skills. One does not have to recapitulate the trial-and-error, lucky accidents, or strokes of genius of other individuals but can build on their discoveries, avoiding the proverbial waste of reinventing the wheel.

Language not only lowers the cost of acquiring a complex skill but multiplies the benefit. The knowledge not only can be exploited to manipulate the environment, but it can be shared with kin and other cooperators. Indeed, among commodities, information is unusually conducive to being shared because it is what economists call a "nonrival good": it can be duplicated without loss. If I give you a fish (a rival good), I no longer have the fish; as the saying might have gone, you cannot eat your fish and have it. But if I teach you to fish, it does not mean that I am now amnesic for the skill of fishing; that valuable commodity now exists in twice as many copies. Language can multiply this proliferation: for the minor cost of a few seconds of breath, a speaker can confer on a listener the invaluable benefit of a new bit of know-how. Crucially, a commodity that confers a high benefit on others at a low cost to the self is a key ingredient in the evolution of cooperation by reciprocal altruism, because both parties can profit from their exchange over the long run (Trivers, 1971). The ability to share know-how through language thus may have been a major accelerant in the evolution of cooperation because it gives humans both the incentive and the means to cooperate. People can trade not only goods but know-how and favors, and the negotiations are not limited to what can be exchanged there and then but to goods and favors transferred at widely separated times.

Language may foster cooperation, but it also depends on it, because there is no advantage in sharing information with adversaries (as we see in the expression "to be on speaking terms"). The inherent synergies among language, intelligence, sociality, enhanced paternal and grandmaternal investment, extended lives and childhoods, and diverse habitats and food sources suggest that these features cohere as a characterization of the cognitive niche, with enhancements in each serving as an additional selection pressure for the others. As far as timing is concerned, we would expect that the corresponding adaptations coevolved gradually, beginning with the first hominid species that possessed some minimal combination of preconditions (e.g., bipedality, group living, omnivory), increasing in

complexity through the lineage of species that showed signs of tool use, cooperation, and anatomical adaptations to language, and exploding in behaviorally modern *H. sapiens*.

## EVALUATING THE THEORY OF THE COGNITIVE NICHE

The theory of the cognitive niche, I believe, has several advantages as an explanation of the evolution of the human mind. It incorporates facts about the cognitive, affective, and linguistic mechanisms discovered by modern scientific psychology rather than appealing to vague, prescientific black boxes like "symbolic behavior" or "culture." To be specific: the cognitive adaptations comprise the "intuitive theories" of physics, biology, and psychology; the adaptations for cooperation comprise the moral emotions and mechanisms for remembering individuals and their actions; the linguistic adaptations comprise the combinatorial apparatus for grammar and the syntactic and phonological units that it manipulates.

The selection pressures that the theory invokes are straightforward and do not depend on some highly specific behavior (e.g., using projectile weapons, keeping track of wandering children) or environment (e.g., a particular change in climate), none of which were likely to be in place over the millions of years in which modern humans evolved their large brains and complex tools. Instead it invokes the intrinsic advantages of know-how, cooperation, and communication that we recognize uncontroversially in the contemporary world. Science and technology, organizations (such as corporations, universities, armies, and governments), and communication media (such as the press, mail, telephones, television, radio, and the Internet) are, respectively, just the exercise of cognition, sociality, and language writ large, and they singly and jointly enable the achievement of outcomes that would be impossible without them. The theory of the cognitive niche simply extrapolates these advantages backward in time and scale.

Moreover, the theory requires no radical revision to evolutionary theory: neither the teleology and creationism of Wallace, nor mechanisms that are exotic, extreme, or invoked ad hoc for our species. Although grammatical language is unique to humans, and our intelligence and sociality are hyperdeveloped, it is not uncommon for natural selection to favor unique or extreme traits, such as the elephant's trunk, the narwhal's tusk, the whale's baleen, the platypus's duckbill, and the armadillo's armor. Given the undeniable practical advantages of reasoning, cooperation, and communication, it seems superfluous, when explaining the evolution of human mental mechanisms, to assign a primary role to macromutations, exaptation, runaway sexual selection, group selection, memetics, complexity theory, cultural evolution (other than what we call "history"), or

gene–culture coevolution (other than the commonplace that the products of an organism's behavior are part of its selective environment).

The theory can be tested more rigorously, moreover, using the family of relatively new techniques that detect "footprints of selection" in the human genome (by, for example, comparing rates of nonsynonymous and synonymous base pair substitutions or the amounts of variation in a gene within and across species) (Kreitman, 2000; Przeworski et al., 2000; Bryc et al., Chapter 8, this volume). The theory predicts that there are many genes that were selected in the lineage leading to modern humans whose effects are concentrated in intelligence, language, or sociality. Working backward, it predicts that any genes discovered in modern humans to have disproportionate effects in intelligence, language, or sociality (that is, that do not merely affect overall growth or health) will be found to have been a target of selection. This would differentiate the theory from those that invoke a single macromutation, or genetic changes that affected only global properties of the brain like overall size, or those that attribute all of the complexity and differentiation of human social, cognitive, or linguistic behavior to cultural evolution. It is not necessary that any of these genes affect just a single trait, that they be the *only* gene affecting the trait ("the altruism gene," "the grammar gene," and so on) or that they appear de novo in human evolution (as opposed to being functional changes in a gene found in other mammals). The only requirement is that they contribute to the modern human version of these traits. In practice, the genes may be identified as the normal versions of genes that cause disorders of cognition (e.g., retardation, thought disorders, major learning disabilities), disorders of sociality (e.g., autism, social phobia, antisocial personality disorder), or disorders of language (e.g., language delay, language impairment, stuttering, and dyslexia insofar as it is a consequence of phonological impairment). Alternatively, they may be identified as a family of alleles whose variants cause quantitative variation in intelligence, personality, emotion, or language.

Several recent discoveries have supported these predictions. The gene for the transcription factor FOXP2 is monomorphic in normally developing humans, and when it is mutated it causes impairments in speech, grammar, and orofacial motor control (Vargha-Khadem et al., 1998; Lai et al., 2001). The human version shows two differences from the version found in great apes, at least one of them functional, and the ape homolog shows only a single, nonfunctional difference from the one found in mice. The pattern of conservation and variation has been interpreted as evidence for a history of selection in the human lineage (Enard et al., 2002b). In addition, several genes expressed in development of auditory systems differ in humans and chimpanzees and show signs of selection in the human lineage. Because the general auditory demands on humans and chimps

are similar, it is likely that they were selected for their utility in the comprehension of speech (J.D. Clark et al., 2003). And the human *ASPM* gene, which when mutated causes microcephaly and lowered intelligence, also shows signs of selection in the generations since our common ancestor with chimpanzees (Evans et al., 2004b). It is likely that many more genes with cognitive, social, and linguistic effects will be identified in the coming years, and the theory of the cognitive niche predicts that most or all will turn out to be adaptively evolved.

## EMERGENCE OF SCIENCE AND OTHER ABSTRACT ENDEAVORS

Even if the evolution of powerful language and intelligence were explicable by the theory of the cognitive niche, one could ask, with Wallace, how cognitive mechanisms that were selected for physical and social reasoning could have enabled *H. sapiens* to engage in the highly abstract reasoning required in modern science, philosophy, government, commerce, and law.

A key part of the answer is that, in fact, humans *do not* readily engage in these forms of reasoning (Pinker, 1997, 2002, 2007). In most times, places, and stages of development, people's abilities in arithmetic consist of the exact quantities "one," "two," and "many," and an ability to estimate larger amounts approximately (Carey, 2009). Their intuitive physics corresponds to the medieval theory of impetus rather than to Newtonian mechanics (to say nothing of relativity or quantum theory) (McCloskey, 1983). Their intuitive biology consists of creationism, not evolution, of essentialism, not population genetics, and of vitalism, not mechanistic physiology (Atran, 1998). Their intuitive psychology is mind-body dualism, not neurobiological reductionism (Bloom, 2003). Their political philosophy is based on kin, clan, tribe, and vendetta, not on the theory of the social contract (Daly and Wilson, 1988). Their economics is based on tit-for-tat back-scratching and barter, not on money, interest, rent, and profit (Fiske, 2004). And their morality is a mixture of intuitions of purity, authority, loyalty, conformity, and reciprocity, not the generalized notions of fairness and justice that we identify with moral reasoning (Haidt, 2002).

Nonetheless, *some* humans were able to invent the different components of modern knowledge, and all are capable of learning them. So we still need an explanation of how our cognitive mechanisms are capable of embracing this abstract reasoning.

The key may lie in a psycholinguistic phenomenon that may be called *metaphorical abstraction* (Jackendoff, 1978; Lakoff and Johnson, 1980; Talmy, 2000; Pinker, 2007). Linguists such as Ray Jackendoff, George Lakoff, and Len Talmy have long noticed that constructions associated with concrete

scenarios are often analogically extended to more abstract concepts. Consider these sentences:

1. a. The messenger went from Paris to Istanbul.
   b. The inheritance went to Fred.
   c. The light went from green to red.
   d. The meeting went from 3:00 to 4:00.

The first sentence (a) uses the verb *go* and the prepositions *from* and *to* in their usual spatial senses, indicating the motion of an object from a source to a goal. But in 1.b, the words are used to indicate a *metaphorical* motion, as if wealth moved in space from owner to owner. In 1.c the words are being used to express a change of state: a kind of motion in state-space. And in 1.d they convey a shift in time, as if scheduling an event was placing or moving it along a time line.

A similar kind of extension may be seen in constructions expressing the use of force:

2. a. Rose forced the door to open.
   b. Rose forced Sadie to go.
   c. Rose forced herself to go.

Sentence 2.a conveys an instance of physical force, but 2.b conveys a kind of metaphorical *interpersonal* force (a threat or wielding of authority), and 2.c an *intrapersonal* force, as if the self were divided into agents and once part could restrain or impel another.

Tacit metaphors involving space and force are ubiquitous in human languages. Moreover, they participate in the combinatorial apparatus of grammar and thus can be assembled into more complex units. Many locutions concerning communication, for example, employ the complex metaphor of a sender (the communicator) putting an object (the idea) in a container (the message) and causing it to move to a recipient (the hearer or reader): We *gather* our ideas to *put* them *into* words, and if our words are not *empty* or *hollow*, we might *get* these ideas *across to* a listener, who can *unpack* our words to *extract* their *content* (Reddy, 1993).

These metaphors could be, of course, nothing but opaque constructions coined in rare acts of creation by past speakers and memorized uncomprehendingly by current ones. But several phenomena suggest that they reflect an ability of the human mind to readily connect abstract ideas with concrete scenarios. First, children occasionally make errors in their spontaneous speech, which suggest they grasp parallels between space and other domains and extend them in metaphors they could not have memorized from their parents. Examples include *I putted part of the sleeve*

*blue* (change of location → change of state), *Can I have any reading behind the dinner*? (space → time), and *My dolly is scrunched from someone . . . but not from me* (source of motion → source of causation) (Bowerman, 1983; Pinker, 1989). Second, several experiments have shown that when people are engaged in simple spatial reasoning it interferes with their thoughts about time and possession (Pinker, 2007). Third, adults often experience episodes of spontaneous reminding in which an idea was activated only because it shared an abstract conceptual structure with the reminder, rather than a concrete sensory feature. For example, an episode of a barber not cutting a man's hair short enough may remind him of a wife not cooking his steak well enough done. A futile attempt at evenly darkening successive regions of a photo in Photoshop may remind a person of a futile attempt to level a wobbly table by successively cutting slices off each of its legs (Schank, 1982; Hofstadter, 1995; Pinker, 2007). This process of analogical reminding may be the real-time mental mechanism that allows cognitive structures for space, force, and other physical entities to be applied to more abstract subject matter.

The value of metaphorical abstraction consists not in noticing a poetic similarity but in the fact that certain logical relationships that apply to space and force can be effectively carried over to abstract domains. The position of an object in space is logically similar to the value of a variable, and thus spatial thinking can be co-opted for propositional inferences. In the realm of space, if one knows that A moves from X to Y, one can deduce that A is now at Y, but was not at Y in the past. An isomorphic inference may be made in the realm of possession: If A is *given* by Michael to Lisa, it is now *owned* by Lisa, but was not owned by her in the past.

A similar isomorphism allows reasoning about force to be co-opted for reasoning about abstract causation, because both support counterfactual inferences. If A forces B to move from X to Y, then if A had not forced it, B would still be at X. Similarly, If Michael forced Lisa to be polite to Sam, then if Michael had not forced her, she would not have been polite to Sam.

The value of a variable (which is parallel to position in space) and the causation of change (which is parallel to the application of force) are the basic elements of scientific thinking. This suggests that a mind that evolved cognitive mechanisms for reasoning about space and force, an analogical memory that encourages concrete concepts to be applied to abstract ones with a similar logical structure, and mechanisms of productive combination that assemble them into complex hierarchical data structures, could engage in the mental activity required for modern science (Pinker, 1997, 2007; Gentner, 2003). In this conception, the brain's ability to carry out metaphorical abstraction did not evolve to coin metaphors in language, but to multiply the opportunities for cognitive

inference in domains other than those for which a cognitive model was originally adapted.

Evidence from science education and the history of science suggest that structured analogies and other mental reassignments in which a concrete domain of cognition is attached to a new subject matter are crucial to the discovery and transmission of scientific and mathematical ideas (Gentner and Jeziorski, 1989; Boyd, 1993; Spelke, 2003; Carey, 2009). Children learn to extend their primitive number sense beyond "one, two, many" by sensing the analogies among an increase in approximate magnitude, position along a line, and the order of number words in the counting sequence. To learn chemistry, people must stretch their intuitive physics and treat a natural substance not as having an essence but as consisting of microscopic objects and connectors. To understand biology, they put aside the intuitive notions of essences and vital forces and think of living things the way they think of tools, with a function and structure. To learn psychology and neuroscience, they must treat the mind not as an immaterial soul but as the organ of a living creature, as an artifact designed by natural selection, and as a collection of physical objects, neurons.

Wallace, recall, also wondered about the human ability to participate in modern institutions such as governments, universities, and corporations. But like humans' puzzling ability to do science, their puzzling ability to take part in modern organizations is partly a pseudoproblem, because in fact the rules of modern institutions do not come naturally to us.

Sociality in natural environments is based on concepts and motives adapted to kinship, dominance, alliances, and reciprocity. Humans, when left to their own devices, tend to apply these mindsets within modern organizations. The result is nepotism, cronyism, deference to authority, and polite consensus—all of which are appropriate to traditional small-scale societies but corrosive of modern ones.

Just as successful science requires people to reassign their cognitive faculties in unprecedented ways, successful organizations require people to reassign their *social* faculties in evolutionarily unprecedented ways. In universities, for example, the mindset of communal sharing (which is naturally applied to food distribution within the family or village) must be applied to the commodity of ideas, which are treated as resources to be shared rather than, say, traits that reflect well on a person, or inherent wants that comrades must respect if they are to maintain their relationship. The evaluation of ideas also must be wrenched away from the mindset of authority: department chairs can demand larger offices or higher salaries but not that their colleagues and students acquiesce to their theories. These radically new rules for relationships are the basis for open debate and peer review in scholarship, and for the checks and balances and accounting systems found in other modern institutions (Pinker, 2007).

## CONCLUSION

The evolution of the human mind is such a profound mystery that it became the principal bone of contention between the two codiscoverers of the theory of natural selection. It has been an impetus to creationism and spiritualism in their day and in ours, and continues to be a source of proposed complications and elaborations of evolutionary theory. But in a year celebrating Darwin's life and work, it would be fitting to see if the most parsimonious application of his theory to the human mind is sufficient, namely that the mind, like other complex organs, owes its origin and design to natural selection.

I have sketched a testable theory, rooted in cognitive science and evolutionary psychology, that suggests that it is. According to this theory, hominids evolved to specialize in the cognitive niche, which is defined by: reasoning about the causal structure of the world, cooperating with other individuals, and sharing that knowledge and negotiating those agreements via language. This triad of adaptations coevolved with one another and with life-history and sexual traits such as enhanced parental investment from both sexes and multiple generations, longer childhoods and life spans, complex sexuality, and the accumulation of local knowledge and social conventions in distinct cultures.

Although adaptations to the cognitive niche confer obvious advantages in any natural environment, they are insufficient for reasoning in modern institutions such as science and government. Over the course of history and in their own educations, people accommodate themselves to these new skills and bodies of knowledge via the process of metaphorical abstraction, in which cognitive schemas and social emotions that evolved for one domain can be pressed into service for another and assembled into increasingly complex mental structures.

# 14

# A Role for Relaxed Selection in the Evolution of the Language Capacity

TERRENCE W. DEACON

Explaining the extravagant complexity of the human language and our competence to acquire it has long posed challenges for natural selection theory. To answer his critics, Darwin turned to sexual selection to account for the extreme development of language. Many contemporary evolutionary theorists have invoked incredibly lucky mutation or some variant of the assimilation of acquired behaviors to innate predispositions in an effort to explain it. Recent evodevo approaches have identified developmental processes that help to explain how complex functional synergies can evolve by Darwinian means. Interestingly, many of these developmental mechanisms bear a resemblance to aspects of Darwin's mechanism of natural selection, often differing only in one respect (e.g., form of duplication, kind of variation, competition/cooperation). A common feature is an interplay between processes of stabilizing selection and processes of relaxed selection at different levels of organism function. These may play important roles in the many levels of evolutionary process contributing to language. Surprisingly, the relaxation of selection at the organism level may have been a source of many complex synergistic features of the human language capacity, and may help explain why so much language information is "inherited" socially.

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Language is both a social and biological phenomenon. The capacity to acquire and use it is a unique and distinctive trait that evolved in only one species on Earth. Its complexity and organization are like nothing else in biology, and yet it is also unlike any intentionally designed social convention. Short of appealing to divine intervention or miraculous accident, we must look to some variant of natural selection to explain it. By paying attention to the way Darwin's concept of natural selection can be generalized to other systems, and how variants on this process operate at different interdependent levels of organism function, explaining the complexity of language and the language adaptation can be made more tractable.

Darwin's theory of natural selection is based on three widely acceptable characteristics of organism reproduction. In the early winter of 1838, after reading Thomas Malthus' "Essay on Population," Charles Darwin wrote the following lines in his E Notebook: "Three principles will account for all: (1) Grandchildren like grandfathers; (2) Tendency to small change . . . especially with physical change; (3) Great fertility in proportion to support of parents" (Darwin, 1838, p. 58).

In the most general terms, these correspond to duplication-multiplication, spontaneous variation from the original, and the surfeit of reproduction that will inevitably reduce this variety via competition for scare resources. Darwin's final refinement was to recognize that, given inevitable culling, the conditions of survival (and particularly, reproduction) would differentially reduce this variety in a way that favored variant traits best suited for that context—adaptation. Darwin recognized that *irrespective of the mechanisms involved,* if these conditions are present, a lineage will tend to become adapted to local conditions if given sufficient time and generations. This was a remarkably simple recipe for biological change, and yet its implications were enormous and counterintuitive. As one critic of *On the Origin of Species* (Darwin, 1859) was to write: "In the theory with which we have to deal, Absolute Ignorance is the artificer; so that we may enunciate as the fundamental principle of the whole system, that, in order to make a perfect and beautiful machine, it is not requisite to know how to make it" (MacKenzie, 1868, p. 217).

Adaptation is the natural counterpart to functional design, but the idea that exquisite biological design might be achieved in the absence of any information about the context of use seemed absurd. Deeply ingrained intuitions, gained through the difficult experience of designing and constructing even simple artifacts and machines, made it unquestionable that only considerable planning and knowledge about the relevant properties of the materials and tasks involved could yield reliable functional outcomes. Moreover, the difficulties encountered multiply geometrically with increasing complexity because of the way that changing one component

can interfere with the relationships to others. Given the fact that organisms are constituted by vastly many complicated systems of chemical and cellular interactions, this difficulty has led critics to conclude that precisely because it is a blind and mindless mechanism it should be less capable of giving rise to adaptive functionality the more complex the system. Thus, such highly complex functional capacities as human cognition and language would intuitively seem to be the least evolvable of life's products. Indeed, so-called "intelligent design" critiques of Darwinism have focused on far simpler molecular and cellular mechanisms to make their argument that the complexity of organism design is not evolvable, indirectly implying that our vastly more complex cognitive abilities are all the more beyond the explanatory power of natural selection theory.

For these reasons, since Darwin's time, the human language capacity has been a perennially cited paragon of extreme complexity that defies the explanatory powers of natural selection. And it is not just critics of Darwinism who have argued that this most distinctive human capacity is problematic. Alfred Russel Wallace—the codiscoverer of natural selection theory—famously argued that the human intellectual capacity that makes language possible is developed to a level of complexity that far exceeds what is achievable through natural selection alone. While fiercely defending natural selection theory with respect to the traits of other species, he argued that in the case of humans, "natural selection could only have endowed the savage with a brain a little superior to that of an ape" (Wallace, 1869, p. 392). And Charles Lyell—who personally promoted Darwin's work and generally supported the evolutionary perspective—also worried that language was just too complex to have evolved by natural means (Lyell, 1863; Bynum, 1984). The vast vocabulary and baroquely structured grammar and syntax of even the simplest of natural languages is orders of magnitude more complex than any other species' communication system, and the capacity this provides for expressing highly esoteric concepts and conveying aesthetic experiences seems far removed from anything with direct adaptive consequence.

Despite the unimpeachable success of Darwinian theory in the 150 years that have elapsed since the publication of *On the Origin of Species* (Darwin, 1859), language still poses challenges for evolutionary biology. The challenge is probably best exemplified by how language origin is still being explained by many highly respected theorists. Take for example Noam Chomsky, who is arguably the most influential linguist of the 20th century. He has reasoned that human language competence could not have been the product of natural selection, even though he believes that it evolved as an inherited biological trait. Its special features, such as its recursive organization, and the often-baroque ways this property is reflected in the various acceptable and unacceptable syntactic opera-

tions of a given language, do not, according to him, facilitate any communicative function (Chomsky, 1986). Indeed they seem on the surface to be reflections of a tendency for systematization of language-unique principles of structural coherence and systemic consistency that may have more to do with the generativity of thought than with communication (Chomsky, 2005). Few if any of these features can be justified in terms of any direct contribution to reproductive benefit.

Of course, nonadaptive traits, functional compromises, and inefficiency are also common to other biological adaptations. So this does not in itself disqualify the human language faculty as a biological adaptation honed by natural selection. But an innate capacity that appears to be highly complex in ways that mostly tend to impede functional utility requires special explanation.

Chomsky's nonadaptationist view is not, however, widely accepted, even by those who otherwise promote his strong nativist approach to linguistic theory. For example, Steven Pinker (1994) has eloquently argued that the structural complexity of language implicitly demands a natural selection explanation. He echoes the general assumption that *only* the process of natural selection can generate such well-fitted functional complexity in biology. No mere side effect or accidental genetic damage can be expected to exhibit anywhere near the complexity and utility of language or the human predisposition to acquire it. The very complexity of this capacity is thus taken as evidence of the operation of extensive natural selection.

Darwin himself fretted over the possibility that natural selection alone might be incapable of accounting for exaggerated functional complexity in nature. In a letter he wrote to Asa Gray shortly after the publication of *On the Origin of Species* (Darwin, 1859), he admits that "the sight of a feather in a peacock's tail, whenever I gaze at it, makes me feel sick!" (Darwin, 1860). Despite the spectacular and elaborately formed details of this adornment, it was a burden that negatively impacted health and survival and so could not have been subject to natural selection with respect to the environment. But it was the extravagance of traits such as this, despite their lack of utility, which suggested to Darwin an approach to the challenge of explaining human mental capacities.

In the case of the peacock tail, and other similar traits, Darwin realized that, indeed, something other than natural selection with respect to environmental conditions was responsible. Recognizing that reproduction rather than individual survival was the critical factor in evolution, he argued that competition with respect to reproductive access (sexual selection) could result in runaway selection on certain traits, independent of their environmental suitability. Darwin argued that a display feature or fighting ability that led an individual to outcompete others in

gaining access to mates would also favor proliferation and evolutionary exaggeration of these traits, even at some cost to individual health and survival. Analogously, he postulated that selection with respect to sex might also explain such extravagant and highly divergent traits as human language. In his book *The Descent of Man and Selection in Relation to Sex* (Darwin, 1871a)—which is typically referred to by only the first half of its title—Darwin argues that language and other human traits that appear exaggerated beyond survival value can be explained as consequences of sexual selection. So, for example, he imagines that language might have evolved from something akin to birdsong, used as a means to attract mates, and that the ability to produce highly elaborate vocal behaviors was progressively exaggerated by a kind of arms-race competition for the most complex vocal display.

Unfortunately, Darwin's speculations in this respect were most effectively criticized by the worst of all possible opponents: the codiscoverer of natural selection, Alfred Russel Wallace. Wallace was scandalized by Darwin's sexual selection theory, considering it Darwin's greatest error, because it appeared to admit a subjective factor into evolutionary theory. Indeed, it appeared to elevate aesthetic appreciation to the status of a significant factor in evolution. Wallace's alternative theory to account for exaggerated display traits relied instead on explanations that invoked incidental physiological mechanisms in males and the need to suppress their effects in females, to avoid predation. But when combined with his strong anti-Lamarckian views, Wallace's denial of Darwin's sexual selection account of these extreme human traits appeared to leave him with no other conceivable mechanism capable of explaining them. He instead abandoned a physical account altogether and infamously invoked a spiritual influence, suggesting that "some intelligent power has guided or determined the development of man" (Wallace, 1870a, p. 350).

Wallace was of course wrong in his denial of the plausibility of sexual selection, although not completely wrong to doubt that aesthetic appreciation or combative prowess were the primary factors. It took a century to recognize that the theory needed to be based instead on asymmetries of parental investment in offspring care between the sexes (Trivers, 1972). Today, sexual selection theory is again considered an important adjunct to the theory of natural selection; however, its reinstatement has not resuscitated the power of Darwin's account of language origins.[1] Even though Wallace's critique of sexual selection has been answered and its power to explain the evolution of certain exaggerated traits is now recognized, there

[1] There are, nevertheless, contemporary theorists who have offered variants on Darwin's proposed sexual selection account of language origins [see, e.g., G. Miller (1999), Burling (2005), and Locke and Bogin (2006)].

are strong reasons for doubting its relevance to this most distinctive of human traits. This is because sexual selection inevitably produces complementary divergence of male and female traits, as is exemplified by peacock tails and moose antlers, which are exhibited only by males. Though there are indeed a few highly divergent traits distinguishing women from men (e.g., patterns of fat deposition in breasts and hips, etc.), the sexes differ only very subtly in their intellectual and language abilities. Therefore, accounting for the extravagant complexity of language in terms of sexual selection requires explaining why it lacks this otherwise ubiquitous mark of extreme sexual dimorphism.

For the most part, however, worries about the sufficiency of natural selection theory to account for our language capacity have simply been ignored by contemporary theorists. Some of the more prominent approaches to the origins of language avoid the issue of selection altogether by attributing this ability to an astonishingly lucky accident of genetic mutation. Previously, it was noted that Chomsky has attributed this unique capacity to a salutatory event in which this ability arose suddenly and irrespective of honing by natural selection. But archeologists such as Mellars (1996) and Klein (2002), noting the explosion of cultural variations of stone tool technologies and the first appearance of decorative and representational forms (such as beads, carvings, and cave paintings) between 60,000 and 30,000 years ago, have argued that a sudden major change in brain function (a mutational accident that Klein has characterized as "the brain's Big Bang") could explain this apparent appearance of recognizably modern human activities.

This willingness to appeal to lucky accident as the primary explanation for this distinctive trait is in many respects a symptom of the problem, not an explanation. Worse, it is an approach that could easily backfire. The appeal to pure accident (e.g., a "hopeful monster" mutation) to explain the evolution of such a highly complex and distinctive trait is the biological equivalent of invoking a miracle. Although neo-Darwinism is indeed based on the assumption that accidental genetic changes contribute to the phylogenetic diversification of traits, this does not imply that complex functional organization arises by accident. This overemphasis on the creative role of variation reflects a tendency to downplay the fact that what varies must be generated by processes of reproduction and development. It is the spontaneous variation of these generative processes that provides the raw material from which natural selection sculpts, so to speak, and so the properties of these generative mechanisms must also be considered. This expansion of focus has given rise to a view of the evolutionary process often called evodevo, because it specifically takes account of the constraining and biasing influences of these generative processes. Highlighting this aspect of the evolutionary process will be the focus of this essay.

To explain the origin of the highly structured human-unique adaptation inevitably requires addressing Wallace's challenge concerning the complexity and apparent nonadaptive aspects of these features. It is significant, then, that theorists who view language functions as products of natural selection have turned to a somewhat indirect variant of the theory to account for the many details of language structure. Most commonly, this is involves an appeal to what has come to be called the "Baldwin effect" after one of its late 19th-century architects, James Mark Baldwin (1896).[2] This was a variant of natural selection theory that theoretically might lead to pseudo-Lamarckian effects, such that the functional utility of a specific acquired habit of behavior (e.g., a language behavior) could eventually come to be replaced by a fortuitously arising (e.g., via chance mutation) innate analog. The appeal to this theoretical variant of natural selection—which is still a subject of debate concerning both its distinctiveness and presumed efficacy [e.g., Deacon (2003), Federici (2003), Christiansen et al. (2006), Yamauchi (2007)]—exemplifies the special problems that the extravagant complexity of language poses for natural selection.

A variant of this argument is proposed in Deacon (1997), where it is suggested that the regular use of prelinguistic symbolic communication (or protolanguage) created what amounts to a socially constructed artificial niche that in turn imposed novel cognitive demands on hominid brains. This early articulation of what has come to be called "niche construction" theory (Odling-Smee et al., 2003) argues that, analogous to the evolution of beaver aquatic adaptations in response to a beaver-generated aquatic niche, a constellation of learning biases and changes of vocal control evolved in response to the atypical demands of this distinctive mode of communication. To the extent that this mode of communication became important for successful integration into human social groups and a critical prerequisite for successful reproduction, it would bring about selection favoring any traits that favored better acquisition and social transmission of this form of communication. Unlike Baldwinian arguments for the genetic assimilation of grammatical and syntactic features of language, however, the niche construction approach does not assume that acquired language regularities themselves ever become innate. Rather it implicates selection that favors any constellation of attentional, mnemonic, and sensorimotor biases that collectively aid acquisition, use, and transmission of language. Although this could conceivably consist of innate language-specific knowledge, Deacon (1997, 2003) argues that this is less likely than more general cognitive biases that facilitate reliable maintenance of this extrinsic niche. Baldwinian selection can only occur if there is a consistent

[2] Two other theorists are credited with independently proposing the same theory in the same year: Conwy Lloyd Morgan (1896) and Henry Fairfield Osborn (1896, 1897).

and nondistributed genotype–phenotype relationship from person to person and from generation to generation, as well as a significant reproductive consequence of this specific linkage as opposed to others (Federici, 2003; Yamauchi, 2007). Because the particular way that a grammatical category relation or a syntactic operation is instantiated in a given language is arbitrary (e.g., a class of words, word order constraints, inflectional modifications), the evolvability of innate grammatical principles should be only slightly better than for innate words. Thus a recent study by Christiansen et al. (2006) demonstrates that selection affecting the most generic and ubiquitous demands associated with language use, acquisition, and transmission inevitably trumps the weak selection for arbitrarily instantiated language-specific features.

Therefore, although it seems beyond doubt that the human language capacity must have evolved due to extensive selection affecting multiple levels of adaptive mechanisms, both the form of the variant of natural selection that was involved and the nature of the cognitive capacity that it produced remain topics of intense debate in evolutionary biology. Whatever account is given, however, it must explain the evolution of the complex interdependence of the neurological, behavioral, and social transmission features of language. To the extent that we can identify generative biological processes that increase the probability of the expression of synergistic relationships among traits, then, these processes are likely to be relevant to language evolution. We turn to these next.

## EVOLUTION-LIKE PROCESSES IN DEVELOPMENT

Understanding how and why natural selection produces complexity has been significantly advanced by recognizing how Darwinian-like processes that take place at other levels of development and scale contribute. One developmental mechanism that is particularly relevant to the evolution of cognitive complexity is the selection-like process that fine-tunes axonal connection patterns in the developing nervous system. The global organization of mammal brains exhibits a deep conservatism, with common epigenetic mechanisms responsible for their segmental organization and the determination of large-scale connection patterns between regions (Striedter, 1997; O'Leary and Nakagawa, 2002; Mallamaci and Stoykova, 2006). But complementary to this underlying commonality of architecture generated in the early phases of embryogenesis, there is also a later plastic, and more-or-less "regressive" phase of brain development, that contributes to the variations on this general theme (Purves and Lichtman, 1980; Cowan et al., 1984; Wilczynski, 1984; Finlay et al., 1987; Deacon, 1990). The fine-tuning of neural circuitry to match specific body architecture and sensory specializations, and their variations within and between species,

involves a sculpting logic that is loosely analogous to natural selection in a number of ways. The establishment of neural connections by axonal outgrowth and invasion initially involves a somewhat nonspecific phase where axonal guidance is largely controlled by highly conservative attraction, repulsion, and adhesion mechanisms, largely the result of local gene expression effects. This process appears to be fairly species-general, with many mechanisms shared by a wide range of vertebrates.

Although slight tweaks of this species-general brain architecture likely play important roles in producing the structural and functional differences of different species' brains, a significant contribution also comes from selection-like processes that incorporate both intra- and extraorganismic information into the fine-tuning of neural circuitry. The species-general global pattern of connectivity that is under strong but low-resolution genetic guidance becomes the scaffolding for subsequent connectional differentiation in response to signal-mediated activity-dependent competition for synaptic stability (Krubitzer and Kaas, 2005). These competitive interactions appear to follow a Hebbian signal-correlation logic that is characterized by the mnemonic "neurons that fire together wire together." In many systems, the competitive culling of connections is also correlated with neuronal apoptosis ("programmed" cell death). This process produces the fine-scale precision of connection patterns that match the neural populations and topographies of interdependent brain and peripheral structures.

This reflects one of life's general strategies for dealing with the problem of getting a vast array of organism features to achieve good functional integration with one another—effectively adapted to complement one another—with maximum flexibility and minimum design information. A precursor to this idea was proposed in the 1890s by the influential Darwinian and embryologist August Weismann, who is remembered mostly because of his success at repudiating the concept of Lamarckian inheritance. To provide an alternative explanation for features that Lamarckians had assumed would require a use-inheritance process, he suggested that there might be an *intraselection* process occurring in what amounts to the ecosystem of the body (Weismann, 1894). Though differing from what Weissman originally intended, the axonal selection process is indeed a sort of intraorganismic selection process, although its logic differs from natural selection in one important respect: selection of this sort is confined to differential preservation only, not differential reproduction. In this respect, it is like one generation of the operation of natural selection. This more general way of characterizing the distinctive logic of natural selection was characterized by an early advocate of this generalization of Darwinism, Donald T. Campbell (1965), with the phrase "blind variation with selective retention."

This is relevant to the problem of evolvability. In general, the more highly complex, interconnected, and functionally integrated the system, the more likely it will be functionally degraded by structural variation. This is why no one imagines that computer design will be improved by randomly sampling alternative circuit plans. To maintain functional continuity despite local structural changes should require compensatory reorganization throughout. Thus if brain circuits were fully prespecified genetically, they would likely be too fragile to be evolvable.

The role that this intraselection process plays in the adaptive evolution of the brain is exemplified by the brain of the blind mole rat, *Spalax* (Doron and Wollberg, 1994). This fossorial species has vestigial eyes. In its brain, the lateral geniculate nucleus (the thalamic visual nucleus) is "invaded" during development by brainstem auditory and somatic projections that outcompete the sparse projections coming from the small retinas. The projections from the thalamus to the posterior cortex that in other mammals would subserve visual processing instead subserves somatic and auditory functions. Experimental manipulations in other species, in which projections from one sensory modality are reduced in early development, likewise exhibit analogous takeover effects (Frost, 1981; Sur et al., 1988), and manipulations of the sensory periphery likewise demonstrate that intraselection adapts neural functional topography with respect to functional experience. This is a significant contribution to brain evolvability and a general mechanism available for natural selection to recruit. These mechanisms are almost certainly relevant to human brain evolution for language, especially considering that language is such a significant contributor to early experience.

This neuroepigenetic variant of selection logic is only one among many processes that might more generally be described as intraevolutionary mechanisms—that is, intraorganismic morphogenetic processes that parallel attributes characteristic of phylogenetic evolution. Although they each differ in certain respects from natural selection, they all share certain attributes that distinguish them from "design" processes, analogous to the way that natural selection is distinguished from intelligent or end-directed design. First, they involve processes that produce functional integration and/or adaptation even though they are generated by mechanisms that are dissociated from this consequence. Second, they all involve the generation of redundant variant replicas of some prior form (gene, cell, connection, antibody, etc.) brought into interaction with each other and with an external context in a way that allows these differences to affect their subsequent distribution. And third, their preservation and expression are dependent on correlation with context. This highly abstracted analogy to Darwinian logic will be demonstrated by examples to follow, but it can be summarized as this: the replication, variation, and differential preserva-

TABLE 14.1 Parallels Between Evolution-like Processes Between and Within Organisms

| Interorganism | Intraorganism |
|---|---|
| 1. Reproduction and development | 1. Duplication of structure and/or function |
| 2. Divergence via mutation, recombination, and/or drift | 2. Degeneracy and/or dedifferentiation |
| 3. Environment-correlated preservation via superior fittedness | 3. Function-correlated preservation via complementation or synergy |

tion that together characterize natural selection have their counterparts in the redundancy, degeneracy, and functional interdependencies that characterize intraorganismic processes. This parallelism is summarized in Table 14.1.

These intraorganismic parallels to evolutionary processes can be generally distinguished with respect to the level at which selection acts and how this interacts with processes generating functional redundancy. All take advantage of the power of the replicative dynamic of life, expressed in growth and body maintenance as well as in reproduction, because of the redundancy that this produces.

## CASE 1. INTERNAL REDUNDANCY

The paradigm example of a replication–variation–selection dynamic occurring internal to the organism is gene duplication. This intragenomic duplication process has played a critical role in the evolution of organism complexity, and is widely accepted to be a fundamental source of functional synergies at all levels of the organism, from molecular complexes and their interactions to body appendages and their coordination (Ohno, 1970; Li, 1983; Ohta, 1994; Walsh, 1995; Zhang, 2003a). The Darwinian parallels of this intragenomic process are, however, seldom noted. In this process too, duplication allows variants to evolve, but largely because the presence of a redundant copy can relax selection that otherwise would tend to eliminate variant forms with mutations that alter critical functions. Where a redundant copy is not itself a source of maladaptation, single nucleotide substitutions and other noncatastrophic modifications to its sequence tend to progressively and incrementally degrade the functions of its protein product over evolutionary time.

Consider the well-documented case of the hemoglobins (Goodman et al., 1987; Hardison, 1999). Spontaneous duplication of the ancestral hemoglobin gene into the alpha and beta forms allowed each to accumulate mutations that, while maintaining their oxygen-binding function, modified other features of tertiary structure. Independent variations in each form

would originally have accumulated in the population, but sexual recombinations of different forms would have exposed any interaction effects between variants, increasing variants that in combination would have in some way augmented function. The one favorable interaction effect that ultimately evolved to fixation was a complementarity in tertiary shapes that increased the probability of the two variants binding to each other into a 2 × 2 tetrameric form with an improved oxygen-carrying capacity. This synergistic effect thus emerged from a duplication, independent variation, and eventual selection based on fittedness to context (which in this case is the context consisting of the other hemoglobin variant).

In placental mammals the beta hemoglobin was further subject to multiple duplication mutations over the course of evolution. The resulting relaxation of selection has allowed two of these duplicates to degrade to pseudogene status. Four others, however, with slightly variant oxygen-binding characteristics, appear to have been coselected with respect to the different oxygenation demands of fetal life at different stages of gestation, with different variants expressed early and late in fetal development. This different sort of synergy—expressed diachronically rather than synchronically—was also facilitated by relaxed selection, and the way it increased the probability of interaction effects being expressed and thus becoming subject to selection, over and above the function of component genes.

The relaxation of selection that is created by the functional redundancy consequent to gene duplication enables what amounts to a random walk away from the gene's antecedent function. But because a random walk produces incremental deviation, there is a significant nonzero probability that one or more of the increasingly variant forms within a population of organisms will "wander" into a related interaction relationship with some duplicate counterpart, and again become subject to selection for any interactive deleterious or synergistic effects. It is no surprise, then, that gene families descended from a common ancestral gene often form synergistic functional complexes.

The logic of gene duplication is exactly inverted in one respect to that of natural selection. The relaxation of selection produced by internal redundancy reduces competitive elimination, and instead favors preservation of variant forms, thus increasing the random exploration of what might be called adjacent function space. As a result, it increases the probability of encountering both deleterious interactions and synergistic complementarities. Unlike axonal culling or the selective amplification of immune cell replication with respect to antigen presentation, this process occurs phylogenetically rather than ontogeneticically, but the replication, variation, and context-dependent selection takes place within as well as between organisms.

This pattern of duplication, relaxation of selection, functional degradation, and the potential emergence of selection favoring new serendipitous synergistic interactions is replicated at many levels of organism complexity. For example, the duplication and differentiation of regulatory genes, such as the well-studied homeobox-containing genes that control segmental organization in insects and vertebrates via their regulation of the expression of a diverse range of other genes, enables duplication–degradation–complementation at the phenotypic level (Garcia-Fernàndez, 2005; Martindale, 2005). The generation of structural redundancy of body parts (e.g., limbs) via segmental duplication similarly relaxes selection on some with respect to others. Again, this increases the probability that random-walk degradation will expose synergistic possibilities (e.g., of locomotor function) that will become subject to selective stabilization in their own right.

## CASE 2. EXTERNAL REDUNDANCY

Functional duplication that has its origin external to the organism is analogous to gene duplication in influence, but can lead to very different consequences. Without the reliability of internal redundancy, irreversible degradation often follows and can lead to displacement of selection onto other loci that incidentally contribute some role in stabilizing access to the extrinsic source.

Consider the example of the loss of endogenous ascorbic acid (vitamin C) synthesis that has evolved in a few vertebrate lineages. Most vertebrates synthesize ascorbic acid endogenously, because of its important antioxidant functions, but anthropoid primates, fruit bats, guinea pigs, and many birds have lost this capacity (Chatterjee, 1973). Among the primates, all prosimians except Tarsiers also synthesize ascorbic acid endogenously. We, along with other monkeys and apes, must regularly acquire vitamin C from dietary sources: principally fruit. And yet the human genome includes a pseudogene for the final enzyme in the ascorbic acid synthesis pathway: 1-gulono-gamma lactone oxidase (*GULO*) (Nishikimi et al., 1994). The human *GULO* gene (as a likely exemplar of its other anthropoid homologs) has accumulated many randomly distributed substitutions, deletions, and at least one major frame shift effect, which resulted in catastrophic loss of function (Ohta and Nishikimi, 1999).

Presumably, this drift toward degradation of function was a consequence of a change in diet of the ancestors of modern anthropoids to include significant and reliable quantities of fruit. Regular dietary substitution of ascorbic acid from fruit relaxed selection that would otherwise have regularly eliminated mutational variants with reduced ascorbic acid synthesis. Relaxation of this stabilizing selection allowed functional degra-

dation of the *GULO* gene without negative reproductive consequences. But this loss of function resulted in the analog to a form of dietary addiction. Because this essential nutrient was only available extrinsically, selection to maintain its antioxidant function shifted to any sensory biases, behavioral tendencies, and digestive-metabolic mechanisms that increased the probability of obtaining it. What was once selection focused on a single gene locus became fractionally distributed across a great many loci instead. One striking and plausible correlate is the evolution of three-pigment color vision in anthropoid primates, which coincidentally also involves gene duplication effects, the first of which appears to have occurred just before the divergence of Old and New World primates (Shyue et al., 1995; Nei et al., 1997).

## CASE 3. GLOBAL EXTERNAL REDUNDANCY (E.G., DOMESTICATION)

In the rare cases where species enter domains with minimal direct competition (such as invasive founder species) or are otherwise minimally exposed to reproductive and survival limitations (e.g., domestication), the relaxation of selection this produces can result in global dedifferentiation effects. In such conditions, not only should we expect to see redistribution of functional determination, such as characterize cases of specific extrinsic redundancy, but it should be a more or less generalized effect. This should be particularly well exemplified in long-domesticated species such as the domestic dog.

An example of domestication that might shed light on the language origins issue involves domestication of a songbird known as the white-backed munia (Honda and Okanoya, 1999; Okanoya, 2004). Its domesticated cousin is known as the Bengalese finch, which has been bred for coloration in Japan for roughly 250 years. Interestingly, although as far as is known, it was never specifically bred for singing ability (and does not have a particularly sonorous song), the Bengalese finch has a very different singing ability than its wild cousin. Bengalese finches acquire their songs via social learning by copying a particular adult singer or singers. As a result, their songs are highly variable within and between individuals. In contrast, the white-backed munia does not learn its song from others and has an autonomously developed and highly rigid song.

Birdsong, like other forms of display complexity, are generally assumed to be the result of sexual selection, where it contributes to competition for mates, territory, nest sites, etc. In this case, however, it appears to have complexified in conditions where selection on song function has been

completely relaxed.[3] Variability can simply be a correlate of degradation of control, and this would indeed be an expected consequence of relaxation of selection; however, the shift from autonomously developed to socially acquired song requires a bit more explanation. In addition, socially acquired song requires the contribution of a significantly larger number of forebrain nuclei and their interconnections than does the production of a mostly innately prespecified song (Jarvis, 2004). This difference also distinguishes the Bengalese finch from the white-backed munia.

Generally, it is assumed than an increase in behavioral complexity and flexibility and an increase in the complexity of neural interactions that support it can only have come about due to intense natural or sexual selection. In this case, however, increased complexity appears to have arisen in the context of global relaxation of selection, and in a remarkably brief period. This apparent paradox can be resolved if we understand the transition in terms of the dedifferentiation and redistribution effects of relaxed selection.

Although data are not currently available to delineate what mechanism generated this difference, its association with an apparent global relaxation of selection suggests the following hypothesis.

By removing the stabilizing effects of natural and sexual selection on song production, the almost exclusive control of song structure by a forebrain nucleus designated RA (robust nucleus of the archistriatum) degraded, as genes maintaining this behavioral template acquired degrading mutations that were not eliminated by selection. As constraints on song generation degraded with prolonged domestication, other neural systems that previously were too weak to have an influence on song structure could now have an effect. These include systems involved in motor learning, conditionally modifiable behaviors, and auditory learning. Because sensory and motor biases can be significantly affected by experience, song structure could also become increasingly subject to auditory experience and the influence of social stimuli. In this way, additional neural circuit involvement and the increased importance of social transmission in the determination of song structure can be reflections of functional dedifferentiation, and yet can also be sources of serendipitous synergistic effects as well. The result is a tendency to shift control of a previously innate and localized function onto a distributed array of systems that each now only fractionally influences that function. This effectively offloads a significant

[3] Although it is possible that song complexity was inadvertently selected either by unconscious bias during breeding or because of linkage, epistatic, or pleiotropic association with the genetics of coloration, no evidence for such a coupling exists. And in addition, each of these theories makes unusual assumptions that are not required for the relaxed selection account. Genetic analysis will be required to ultimately choose between these mechanisms.

degree of genetic control onto epigenetic processes, and because of their openness to experiential modification, it increasingly opens the door to the influence of social transmission (Deacon, 2009).

There are a number of features that distinguish the neurology of linguistic communication from that of the major forms of vocal communication in other primates (and mammals in general) that appear to have parallels in the finch/munia case. These include (*i*) a significant decrease in the specific arousal-coupling of vocal behaviors; (*ii*) minimization of constraint on the ordering and combinations of vocal sounds; (*iii*) reduction, simplification of the innate call repertoire; (*iv*) subordination of innate call features to a secondary role in emotional tone expression via speech prosody; (*v*) a significantly increased role of auditory learning via social transmission; (*vi*) widely distributed synergistic forebrain control of language compared with highly localized subcortical control of innate vocalizations; and, of course, (*vii*) an increased social-cognitive regulation of the function of vocal communication (Deacon, 2009).

This raises an obvious question: Could humans be a self-domesticated species—that is, a degenerate ape? The munia/finch analogy suggests that genetic dedifferentiation affecting the nervous system may have contributed to functional complexity in human language evolution. Has there been more widespread degeneration as well? If so, it might help explain the extensive human cognitive–social–emotional flexibility compared with other mammalian species. Could human mental plasticity, cultural variability, aesthetic and religious sensibilities, and susceptibility to social control and conformity be an expression of cognitive–emotional dedifferentiation?

## PUTTING HUMPTY DUMPTY TOGETHER AGAIN

This exploration of intraorganism parallels to evolutionary processes of selection and drift has highlighted a number of mechanisms by which remarkably complex synergistic relationships can emerge serendipitously in the course of evolution. These processes are not exclusive of the effects of natural and sexual selection, and in many ways provide auxiliary sources of complex synergy subject to these Darwinian processes. They are almost certainly crucial to the evolvability of highly complex synergistic adaptations, such as human language. Recognition of the potential contributions of each of these processes to evolvability should warn against monolithic natural selection accounts of language evolution that ignore the contributions of these interlinked levels of selection and drift processes.

But language evolution includes one additional twist that may in fact mitigate some fraction of what biological evolutionary mechanisms must explain. Language itself exhibits an evolutionary dynamic that proceeds

irrespective of human biological evolution. Moreover, it occurs at a rate that is probably many orders of magnitude faster than biological evolution and is subject to selective influences that are probably quite alien from any that affect human brains or bodies. Darwin recognized this analogical process, although he did not comment on its implications for human brain evolution.

"A struggle for life is constantly going on amongst the words and grammatical forms in each language. The better, the shorter, the easier forms are constantly gaining the upper hand, and they owe their success to their own inherent virtue" (Darwin, 1871a, p. 91).

The environment that is the source of selection affecting the reproduction and selective elimination of language features is human cognitive limitation and communicative requirements. For this reason, a given language should reflect selection favoring learnability, early acquisition, and ease of use concerning which features are retained or lost over the course of its historical change. In this respect it is an oversimplification to expect that all of the universal design features of language require a biological evolutionary account. So as brains have adapted to the special demands of language processing over hundreds of thousands of years, languages have been adapting to the limitations of those brains at the same time, and a hundred times faster (Deacon, 1997). This means that brain functions selected for the special cognitive, perception, and production demands of language will reflect only the most persistent and invariant demands of this highly variable linguistic niche. This is another reason to expect that the synergistic constellation of human brain adaptations to language will not include specific grammatical content, and to suspect that much of the rich functional organization of any language is subject to influences on this extragenomic form of evolution. In other words, the differential reproduction of language structures through history will be dependent on the fidelity and fecundity of their transmission. Not only will this process be subject to selection with respect to semiotic and pragmatic demands of symbolic communication, it will also favor structures that are more easily acquired by immature brains undergoing activity-dependent intraselection of neural circuitry. Indeed, just as evolvability is aided by evolution-like processes involved in ontogenesis, we should expect that the social evolution of language should itself exhibit analogous processes due to redundancy, degeneracy, and functional interdependency.

Language is too complex and systematic, and our capacity to acquire it is too facile, to be adequately explained by cultural use and general learning alone. But the process of evolution is too convoluted and adventitious to have produced this complex phenomenon by lucky mutation or the genetic internalization of language behavior. These metaphors are more suited to the analysis of a designed artifact. The robusticity of the language

acquisition process, the deep integration of language and human cognition, and the involvement and synergistic interaction of widespread and diverse brain systems in language processes together imply that there has been long-term adaptation involving a very broad suite of genetic loci and the involvement of many levels of intraevolutionary mechanisms. We are more likely to succeed at solving this mystery if we approach it with the expectation that nature produces her most complex works by a logic that is vastly more subtle, and entirely unlike the methods of a watchmaker or computer scientist.

# 15

# Adaptive Specializations, Social Exchange, and the Evolution of Human Intelligence

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Blank-slate theories of human intelligence propose that reasoning is carried out by general-purpose operations applied uniformly across contents. An evolutionary approach implies a radically different model of human intelligence. The task demands of different adaptive problems select for functionally specialized problem-solving strategies, unleashing massive increases in problem-solving power for ancestrally recurrent adaptive problems. Because exchange can evolve only if cooperators can detect cheaters, we hypothesized that the human mind would be equipped with a neurocognitive system specialized for reasoning about social exchange. Whereas humans perform poorly when asked to detect violations of most conditional rules, we predicted and found a dramatic spike in performance when the rule specifies an exchange and violations correspond to cheating. According to critics, people's uncanny accuracy at detecting violations of social exchange rules does not reflect a cheater detection mechanism, but extends instead to all rules regulating when actions are permitted (deontic conditionals). Here we report experimental tests that falsify these theories by demonstrating that deontic rules as a class do not elicit the search for violations. We show that the cheater detection system functions with pinpoint accuracy, searching for violations of social exchange rules only when these are likely to reveal the presence of someone who intends to cheat. It does not search for violations of social exchange rules when these are accidental, when they do not benefit the violator, or when the situation would make cheating difficult.

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To the human mind, certain things seem intuitively correct. The world seems flat and motionless; objects seem solid rather than composed of empty space, fields, and wave functions; space seems Euclidian and 3-dimensional rather than curved and 11-dimensional. Because scientists are equipped with human minds, they often take intuitive propositions for granted and import them—unexamined—into their scientific theories. Because they seem so self-evidently true, it can take centuries before these intuitive assumptions are questioned and, under the cumulative weight of evidence, discarded in favor of counterintuitive alternatives—a spinning Earth orbiting the sun, quantum mechanics, relativity.

For psychology and the cognitive sciences, the intuitive view of human intelligence and rationality—the blank-slate theory of the mind—may be just such a case of an intuition-fueled failure to grapple with evidence (Gallistel, 1990; Tooby and Cosmides, 1992; Cosmides and Tooby, 2001; Pinker, 2002). According to intuition, intelligence—almost by definition—seems to be the ability to reason successfully about almost any topic. If we can reason about any content, from cabbages to kings, it seems self-evident that intelligence must operate by applying inference procedures that operate uniformly regardless of the content domains they are applied to (such procedures are *general-purpose*, *domain-general*, and *content-independent*). Consulting such intuitions, logicians and mathematicians developed content-independent formal systems over the last two centuries that operate in exactly this way. Such explicit formalization then allowed computer scientists to show how reasoning could be automatically carried out by purely "mechanical" operations (whether electronically in a computer or by cellular interactions in the brain). Accordingly, cognitive scientists began searching for cognitive programs implementing logic (Wason and Johnson-Laird, 1972; Rips, 1994), Bayes' rule (Gigerenzer and Murray, 1987), multiple regression (Rumelhart et al., 1986), and other normative methods—the same content-general inferential tools that scientists themselves use for discovering what is true (Gigerenzer and Murray, 1987). Others proposed simpler heuristics that are more fallible than canonical rules of inference [e.g., Gigerenzer et al. (1999), Kahneman (2003)], but most of these were domain-general as well.

Our inferential toolbox does appear to contain a few domain-general devices (Rode et al., 1999; Gallistel and Gibbon, 2000; Cosmides and Tooby, 2001), but there are strong reasons to suspect that these must be supplemented with domain-specific elements as well. Why? To begin with, much—perhaps most—human reasoning diverges wildly from what would be observed if reasoning were based on canonical formal methods. Worse, if adherence to content-independent inferential methods constituted intelligence, then equipping computers with programs implement-

ing these methods, operating at vastly higher rates, should have made them intelligent. It did not. It turns out that general-purpose reasoning methods are very weak, and have crippling defects (e.g., combinatorial explosion) that are a direct consequence of their domain generality (Tooby and Cosmides, 1992; Cosmides and Tooby, 2001; Tooby et al., 2005). Also, content effects (changes in reasoning performance based on changes in content) are ubiquitous (Wason and Johnson-Laird, 1972; Gigerenzer and Murray, 1987) yet difficult to account for in the consensus view. After all, differences in content should make little difference to procedures whose operation is designed to be content-independent. Unfortunately, the effects of content on reasoning have traditionally been dismissed as noise to be ignored rather than a window on reasoning methods of a radically different, content-specific design.

## INTELLIGENCE AND EVOLVED SPECIALIZATIONS

The integration of evolutionary biology with cognitive science led to a markedly different approach to investigating human intelligence and rationality: evolutionary psychology (Tooby and Cosmides, 1992; Cosmides and Tooby, 2001). Organisms are engineered systems that must operate effectively in real time to solve challenging adaptive problems. The computational problems our ancestors faced were not drawn randomly from the universe of all possible problems; instead, they were densely clustered in particular, recurrent families (e.g., predator avoidance, foraging, mating) that occupy only miniscule regions of the space of possible problems. Massive efficiency gains can be achieved when different computational strategies are tailored to the task demands of different problem types. For this reason, natural selection added a diverse array of inferential specializations, each tailored to a particular, adaptively important problem domain (Gallistel, 1990). Freed from the straightjacket of a one-size-fits-all problem-solving strategy, these reasoning specializations succeed by deploying procedures that produce adaptive inferences in a specific domain, even if these operations are invalid, useless, or harmful if activated outside that domain. They can do this by exploiting regularities—content-specific relationships—that hold true within the problem domain, but not outside of it. This approach naturally predicts content effects, because different content domains should activate different inferential rules.

In this view, human intelligence is more powerful than machine intelligence because it contains, alongside general-purpose inferential tools, a large and diverse array of *adaptive specializations*—expert systems, equipped with proprietary problem-solving strategies that evolved to match the recurrent features of their corresponding problem domains.

Indeed, the discovery of previously unknown adaptive specializations proceeded at a rapid pace once cognitive and evolutionary scientists became open to their existence and began to look for them (Tooby and Cosmides, 1992).

For nearly three decades, we have been studying human reasoning in the light of evolution (Cosmides, 1985, 1989; Cosmides and Tooby, 1989, 2005, 2008; Gigerenzer and Hug, 1992; Fiddick et al., 2000, 2005; Stone et al., 2002; Sugiyama et al., 2002; Ermer et al., 2006; Reis et al., 2007). By integrating results from evolutionary game theory with the ecology of hunter-gatherer life, we developed *social contract theory*: a task analysis specifying what computational properties a neurocognitive system would need to generate adaptive inferences and behavior in the social exchange problem domain (Cosmides and Tooby, 1989). We have been systematically testing for the presence of these design features, including an important one: the ability to detect cheaters. Based on these investigations, we have proposed that the human mind reliably develops *social contract algorithms*: a set of programs built by natural selection for reasoning about social exchange (Cosmides, 1985, 1989; Gigerenzer and Hug, 1992; Cosmides and Tooby, 2005, 2008). This system can reason adaptively about social exchange precisely because it does not perform the inferences of any standard formal logic.

## EXCHANGE AS A COMPUTATIONAL PROBLEM

### Selection Pressures for Social Exchange

Two parties can make themselves better off than they were before—thereby increasing their fitness—by exchanging things each values less for things each values more (goods, services, help). Exchange is found in every documented human culture, and takes many forms, such as returning favors, sharing food, and extending acts of help with the (implicit) expectation that they will be reciprocated. Behavioral ecology and hunter-gatherer ethnography have demonstrated that exchange is fundamental to forager subsistence and sociality (Gurven, 2004). Indeed, evidence suggests that certain forms of social exchange were present in hominins at least 2 million years ago (Isaac, 1978). This raises the possibility that selection has introduced computational elements that were well-engineered for social exchange.

### Cognitive Defense Against Cheaters

Selection pressures favoring social exchange exist whenever one organism (the provisioner) can change the behavior of a target organism

to the provisioner's advantage by making the target's receipt of a rationed benefit conditional on the target acting in a required manner. This contingency can be expressed as a *social contract*, a conditional rule that fits the following template: *If you accept benefit B from me, then you must satisfy my requirement R*. The social contract is offered because the provisioner expects to be better off if its conditions are satisfied [e.g., if one gives the theater owner the price of a ticket (*requirement R*) in return for access to the symphony (*benefit B*)]. The target accepts these terms only if the benefit provided more than compensates for any losses he incurs by satisfying the requirement (e.g., if hearing the symphony is worth the cost of the ticket to him). This mutual provisioning of benefits, each conditional on the other's compliance, is what is meant by social exchange or reciprocation (Cosmides, 1985; Cosmides and Tooby, 1989; Tooby and Cosmides, 1996). Understanding it requires a form of conditional reasoning that operates on abstract yet content-specific conceptual elements.

Algorithms generating social exchange require (*i*) a system for representing exchange situations in terms of conceptual primitives such as *agent*, *rationed benefit*, *provisioner's requirement*, and *entitlement*; (*ii*) a system for mapping states of the world onto these proprietary concepts (e.g., the *agent* is the theater owner; the *rationed benefit* is access to the symphony; the *requirement* is payment of the ticket price); and (*iii*) domain-specialized rules of inference that operate on these conceptual primitives, supplying inferences that are necessary to carry out the system's evolved function [rules of logic do not supply the necessary inferences (Cosmides, 1989; Fiddick et al., 2000; Cosmides and Tooby, 2008)].

Adaptations for delivering benefits to unrelated individuals will be selected against unless the losses one incurs by delivering benefits are compensated for by the reciprocal delivery of benefits. Consequently, the existence of cheaters—those who fail to deliver compensatory benefits—threatens the evolution of exchange. Using evolutionary game theory, it has been shown that adaptations for social exchange can be favored and stably maintained by natural selection, but *only if they include design features that enable them to detect cheaters*, and cause them to channel future exchanges to reciprocators and away from cheaters (Trivers, 1971; Axelrod, 1984; Tooby and Cosmides, 1996).

### Cheater Detection Is Person Categorization and Not Event Categorization

Indeed, the exact nature of the adaptive problem posed by cheaters determines how social contract algorithms should have evolved to define the concept *cheater*. A cheater is an agent who (*i*) takes the rationed benefit offered in a social exchange but (*ii*) fails to meet the provisioner's

requirement, and (*iii*) does so by intention rather than by mistake or accident. The evolutionary function of a cheater detection subroutine is to defend the cooperator against exploitation. It is designed to represent and track the other party's behavior so that it can (when warranted) correctly connect an attributed disposition (to cheat) with that particular person (who thereby becomes categorized as a *cheater*). In the experiments reported here, we manipulate these cheater-defining elements and demonstrate that they regulate reasoning about conditional rules involving social exchange.

The conceptual primitive *cheater* along with domain-specific inference rules for detecting cheaters were predicted to be a central part of social exchange reasoning because they are necessary to solve a computational problem that, if unsolved, would prevent the evolution of social exchange. Together, they constitute a logic of social exchange—a content-specialized logic whose conceptual primitives, inference rules, and outputs are quite different from those produced by standard formal logics, such as the predicate calculus. The need for special inferential rules for cheater detection derives from the fact that standard, domain-general conditional reasoning rules will fail to identify cheaters in many circumstances, and will misidentify reciprocators and altruists as cheaters in others (Cosmides, 1989; Gigerenzer and Hug, 1992; Cosmides and Tooby, 2005, 2008).

**Evolutionary Versus Economic and Other Functions**

A cheater is someone who has violated a social contract—a conditional rule involving social exchange—but not all violations of social contracts reveal the presence of a cheater. This fact allows critical tests between an evolutionary and an economic perspective. A commonplace of economics, utility theory, and common sense is that people become adept at solving problems that they are motivated to solve, such as those that have economic consequences. When targets violate a social contract, the provisioner suffers a loss in utility; if these cases are detected, the provisioner could insist on getting what she is owed. If such economic consequences drive the acquisition of reasoning skills, then people should be good at detecting all violations of social contracts because this will allow them to recoup their losses. It would not matter whether the violation occurred by mistake or on purpose, or whether it benefited the violator—the provisioner has suffered a loss in all of these cases. These distinctions do matter, however, if evolution produced a subroutine specialized for detecting cheaters.

The function of a cheater detection subroutine is social categorization: this person=cheater. The fitness benefit that drove the evolution of cheater detection is the ability to avoid squandering costly future coopera-

tive efforts on those who will exploit rather than reciprocate. Violations of social contracts are relevant to this evolved function, but only insofar as they reveal individuals disposed to cheat—that is, individuals who cheat by virtue of their calibration or design. Noncompliance caused by accidental violations and other innocent mistakes do not reveal the disposition to cheat. Hence, they should not be encoded by social contract algorithms as cheating—even though the payoff to the provisioner is the same as cheating. That is, accidental violations may result in someone being cheated (not getting what they are entitled to), but they do not indicate the ongoing menace of a cheater.

Therefore, social contract theory predicts cognitive design features beyond detecting compliance or noncompliance with a social contract. The subroutine should be designed to look for potentially intentional violations, because only these predict future defection and continued exploitation—the negative outcome the system evolved to defend itself against. Indeed, results from evolutionary game theory show that strategies for conditional cooperation do better if they can "see through" failures to reciprocate due to chance, because they continue to reap the benefits of cooperating with other conditional cooperators who may have erred [e.g., Panchanathan and Boyd (2003)]. The surprising social contract prediction—that noncompliance in social exchanges is only detected at high rates when it could reveal cheaters—is tested in the experiments reported below.

### Cue-Based Activation of Cheater Detection

To achieve their large efficiency gains, adaptive specializations should be designed to be differentially activated when they encounter the content domains they are equipped to solve, and inactive when they encounter other content domains where their proprietary operations are inapplicable, mismatched, or invalid (Tooby and Cosmides, 1992; Tooby et al., 2005). This point is central to understanding the logic of the experiments reported here: If there is an evolved inference system specialized for reasoning about social exchange, then the cheater detection subroutine should be differentially activated by content cues signaling the potential for determining whether someone is a cheater. The strategy pursued in these experiments is to add and subtract minimal problem elements that are irrelevant to competing theories of reasoning but that should activate or inactivate the cheater detection subroutine because they allow or interfere with the determination of whether someone is a cheater. The elements we will concentrate on are: (*i*) Is there a *benefit* being rationed? (if not, there is no social exchange); (*ii*) Could the other party benefit by violation of the rule? (if not, then detecting a violation will not identify

a cheater); (*iii*) Did the violator have the intention to cheat? (if not, then detecting a violation will not identify a cheater); and (*iv*) Does the situation make cheating difficult? (if so, then looking for violations is unlikely to reveal cheaters).

## EXPERIMENTAL TESTS OF SOCIAL CONTRACT THEORY

Exchange is, by definition, social behavior that is conditional: The provisioner agrees to deliver a benefit *conditionally* (conditional on the recipient doing what the provisioner required). Engaging in social exchange therefore requires conditional reasoning.

Our experiments use the Wason selection task, a standard tool for investigating conditional reasoning (Wason and Johnson-Laird, 1972). Subjects are given a conditional rule of the form *if P then Q*, and asked to identify possible violations of it—a format that allows one to see how performance varies as a function of the rule's content (Fig. 15.1*A*). It was originally developed to determine whether humans are natural falsificationists—whether the brain spontaneously applies first-order logic to look for cases that might violate a hypothesis or other conditional rule. To their surprise, psychologists found that people perform poorly when asked to solve this simple problem.

According to first-order logic, a conditional rule has the form *if antecedent* (conventionally represented by *P*) *then consequent* (conventionally represented by *Q*). Looking for violations of a conditional rule is a remarkably simple task: According to first-order logic, the rule is violated whenever *P* is true but *Q* is not—that is, by the co-occurrence of *P & not-Q*. For example, the rule "if a person is a biologist, then that person enjoys camping" would be violated by finding a biologist who does not enjoy camping. In a Wason selection task involving this rule, there would be four cards, each representing a different individual. One side would tell whether that individual is a biologist, and the other side would tell whether he or she enjoys camping (see Fig. 15.1). To find out whether the preferences of any of these individuals violate the rule, one would need to investigate the biologist (*P* card) to see if he does not enjoy camping, and the person who does not enjoy camping (*not-Q* card) to see if this person is a biologist. Thus, a fully correct Wason response would be to choose *P*, *not-Q*, and no other cards.

First-order logic is simple to specify—vastly simpler than many other cognitive capacities that humans are known to have, such as vision and grammar acquisition. It is also prototypically content-independent and domain-general: It maps all of the content of conditional rules into the format *if* ***antecedent*** *then* ***consequent***, where the antecedent and consequent can stand for any propositions. It can be informative about nearly

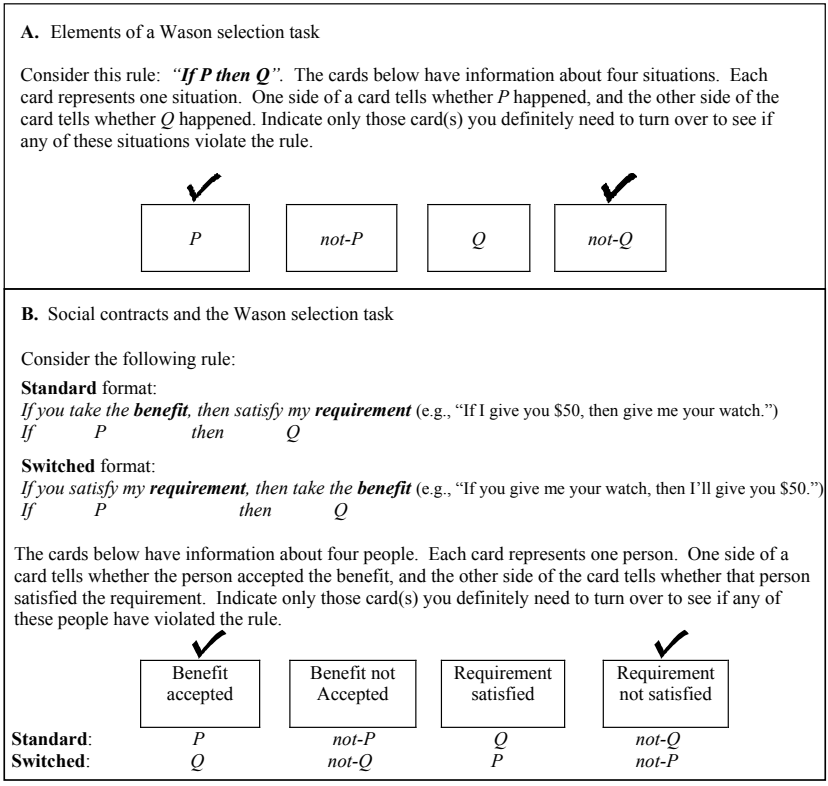


FIGURE 15.1 *(A)* The general structure of a Wason selection task. The rule always has specific content; e.g., "if a person is a biologist, then that person enjoys camping" (an indicative rule). For this rule, each card would represent a different person, reading, for example, "biologist" (*P*), "chemist" (*not-P*), "enjoys camping" (*Q*), "does not enjoy camping" (*not-Q*). The content of the rule can be varied such that the rule is indicative, a social contract, a precaution, a permission rule, or any other conditional of interest, allowing alternative theories of reasoning to be tested. Checkmarks indicate the logically correct card choices. (*B*) General structure of a Wason task when the conditional rule is a social contract. A social contract can be translated into either social contract terms (benefits and requirements) or logical terms (*P*s and *Q*s). Checkmarks indicate the correct card choices if one is looking for cheaters—these should be chosen by a cheater detection subroutine, whether the exchange was expressed in a *standard* format (i.e., *benefit* to potential violator in antecedent clause) or a *switched* format (*benefit* in consequent clause). This results in a logically incorrect answer (*Q & not-P*) when the rule is expressed in the switched format, and a logically correct answer (*P & not-Q*) when the rule is expressed in the standard format. Tests of switched social contracts have shown that the reasoning procedures activated cause one to detect cheaters, not logical violations. Note that a logically correct response to a switched social contract—where *P = requirement satisfied* and *not-Q = benefit not accepted*—would fail to detect cheaters.

everything. Finally, the inferential rules of first-order logic are incapable of responding differentially to particular contents, because they do not represent content at all. All its rules see are its conceptual primitives (e.g., *antecedent*, *consequent*, *if*, *then*).

The biologist-camping rule is *indicative*: It claims to indicate or describe some relationship in the world. Given an indicative conditional, only 5–30% of normal subjects respond with the logically correct answer, *P & not-Q*. Most do choose *P*, but about half omit *not-Q*, many choose *Q*, and a few choose *not-P.* Although one might think that people would learn to reason correctly about familiar relationships, performance remains poor even when the indicative rule involves very familiar content drawn from direct experience—such as, *if I eat cereal, then I drink orange juice* (Wason, 1983; Cosmides, 1985). Either our species did not evolve a full and unimpaired version of first-order logic, or significant parts of it are not activated when people try to solve this simple information search task.

Although originally designed to test whether people had a content-general system for conditional reasoning, the Wason task can be and has been used to test many of the predictions of social contract theory [for reviews, see Cosmides and Tooby (2005, 2008)]. The hypothesis that the brain contains social contract algorithms predicts that reasoning performance should shift when it encounters social exchange content. In particular, it predicts a sharply enhanced ability to reason adaptively about conditional rules when those rules specify a social exchange.

Content is indeed decisive. Although performance on the Wason selection task is typically poor, when the conditional rule involves social exchange and detecting a violation corresponds to looking for cheaters, 65–80% of subjects correctly detect violations (Cosmides, 1985, 1989; Gigerenzer and Hug, 1992; Cosmides and Tooby, 2005, 2008). Confounding the idea that people improve only with increasing experience, subjects perform well even when the conditional rule specifies a wildly unfamiliar social contract that no subject has ever heard before (e.g., "if you get a tattoo on your face, then I'll give you cassava root"). Indeed, we have found no difference in performance between totally unfamiliar social contracts and thoroughly familiar ones. Moreover, the ability to detect cheaters on social contracts is present as early as it can be tested (ages 3–4) (Harris et al., 2001). Consistent with the hypothesis that this adaptive specialization is part of our species' cognitive architecture, this pattern of results has been found in every culture where it has been tested, from industrialized market economies to Shiwiar hunter horticulturalists of the Ecuadorian Amazon (Sugiyama et al., 2002).

Because the correct answer if one is looking for cheaters is sometimes the logically correct answer as well, many people misunderstand us to be claiming that social exchange content boosts *logical* reasoning. But social

exchange activates nonstandard rules of inference that diverge sharply from first-order logic. The adaptively correct answer when one is looking for cheaters is to choose cards representing people who have *taken the benefit* and ***not*** *met the requirement*, regardless of the logical category into which these fall. It is possible to create social exchange problems in which these correspond to a logically incorrect answer: *Q & not-P* (see Fig. 15.1*B*). When this was done, subjects' selections matched the predictions of the nonstandard evolutionary logic of social exchange and violated first-order logic. *Q* and *not-P* choices were predicted from first principles, and had never been predicted by any other theory, or previously elicited (Cosmides, 1985, 1989; Gigerenzer and Hug, 1992).

**Deontic Logic or Social Contract Algorithms?**

Most reasoning researchers now concede that (*i*) content effects for social exchanges are real, replicable, and robust; and (*ii*) first-order logic cannot explain how people reason about social exchange. However, they continue to resist the counterintuitive notion that reasoning in this domain is governed by an adaptive specialization. Instead, they propose that reasoning about social exchange is governed by some version of deontic logic—a formal system for reasoning about concepts such as permission and obligation. Social contracts do involve deontic concepts, so this is a plausible proposal. However, the universe of deontic rules is far larger than social contracts, extending to moral rules, imperatives, norms, and so on. If the mind comes equipped with (or acquires) some form of deontic logic, then people should be good at detecting violations of all deontic rules (Cheng and Holyoak, 1985; Fodor, 2000), or at least those involving utilities (Manktelow and Over, 1990, 1991; Sperber et al., 1995).

In support of the deontic position, its advocates point out that another type of deontic conditional that we and others have worked on also elicits good violation detection on the Wason task: precautionary rules (Cheng and Holyoak, 1989; Manktelow and Over, 1990; Fiddick et al., 2000; Stone et al., 2002; Ermer et al., 2006). These are conditionals that fit the template "*if one is to engage in hazardous activity H, then one must take precaution R*" (e.g., "if you are working with toxic gases, then you must wear a gas mask"). Precautionary rules are so similar to social contracts that most theories view them as trivial variations on a theme—deontic conditionals involving utilities, processed by precisely the same reasoning system (Cheng and Holyoak, 1989; Manktelow and Over, 1990, 1991; Kirby, 1994; Oaksford and Chater, 1994; Sperber et al., 1995).

By contrast, evolutionary researchers have proposed that these rules are processed not by social contract algorithms but by a different specialization with a distinct function: to monitor for cases in which people are in

danger by virtue of not having taken the appropriate precaution (Fiddick et al., 2000; Boyer and Lienard, 2006). Neuroimaging results and evidence that brain damage can selectively impair social exchange reasoning (while sparing precautionary reasoning) support the evolutionary hypothesis that these are two distinct specializations, not one superordinate deontic system (Stone et al., 2002; Fiddick et al., 2005; Ermer et al., 2006; Reis et al., 2007). Moreover, an adaptationist perspective predicts that subjects should detect accidental as well as intentional violations of precautionary rules, because both place people in danger—a prediction now tested and confirmed (Fiddick, 2004). By contrast, intentionality should matter in exchanges because unintentional violations do not reveal cheaters—a prediction we test below.

**New Tests Between Deontic and Social Exchange Theories**

In exchange, an agent *permits* another party to take a benefit, conditional upon that party's having met the agent's requirement. There are, however, many situations other than exchange in which an action is permitted conditionally. A *permission rule* is any deontic conditional that fits the template "if one is to take action A, then one must satisfy precondition R" (Cheng and Holyoak, 1985, 1989). According to Cheng and Holyoak's (1985) *permission schema theory*, reasoning about such rules is governed by four production rules that result in people checking the "action taken" card (*P*) and the "precondition not met" card (*not-Q*). We focus on their account because it is the most precisely specified of the deontic accounts. But our experiments also test against all other deontic theories known to us.

It is important to remember that all social contracts are permission rules, but there are many permission rules that are not social contracts. According to permission schema theory, good violation detection is elicited by the entire class of permission rules (Cheng and Holyoak, 1985, 1989)—a far more inclusive and general set that includes precautionary rules, bureaucratic rules, etiquette rules, and social norms, along with social contracts.

Empirically, permission schema theory is undermined or falsified if permission rules that are neither social contracts nor precautions routinely fail to elicit high levels of violation detection. Moreover, social contract theory is supported if social exchange rules (a subset of permission rules) fail to elicit this effect when violation detection does not identify cheaters.

Just how precise and functionally specialized is the reasoning system that causes cheater detection? Below we report the results of four experiments that parametrically test predictions about benefits, intentionality, and the ability to cheat on social contracts. The full text of all Wason tasks tested is available online at www.pnas.org/cgi/content/full/0914623107/

DCSupplemental (hereinafter referred to as SI Text). All experiments had a between-subjects design in which each subject was given a single Wason task. In every case, the rule tested was a permission rule: a deontic conditional that fits the template "if one is to take action A, then one must satisfy precondition R." For the problems tested, the correct answer if one is looking for violations of the rule is to choose the *P* card (action taken), the *not-Q* card (requirement not met), and no others (henceforth *P & not-Q*).

## PERMISSION RULES WITHOUT BENEFITS

The function of a social exchange for each participant is to gain access to a benefit that would otherwise be unavailable to them. Therefore, an important cue that a conditional rule is a social contract is the presence of a desired benefit under the control of an agent—this should activate social contract reasoning. Experiments 1 and 2 compare performance on permission rules that vary a single element: whether *P*, the action to be taken, is a benefit to the potential violator. They show that this has a dramatic effect on performance.

### Experiment 1

Wason tasks consist of a rule and a story setting the context (what the cards refer to, who proposed the rule, and so on). In experiment 1, we kept the stories identical, and made small but theoretically relevant alterations to the rule. By changing *P* to an action that our subjects would spontaneously recognize as a benefit, a permission rule was transformed into a social contract. A two-word change was sufficient (see below, rules 1 and 2).

Experiment 1 compared performance on three permission rules, each described as a law made by a group of tribal elders (SI Text). The story context, which was minimal, was identical for rules 1 and 2, and nearly so for rule 3. The four cards represented what four different members of the tribe had done, and subjects were asked which card(s) they would need to turn over to see whether any of these people had broken the law.

The tribal context allowed the use of permission rules that would be unfamiliar to the subjects (no italics in the originals):

1. "If one is *going out at night*, then one must tie a small piece of red volcanic rock around one's ankle."
2. "If one is *staying home at night*, then one must tie a small piece of red volcanic rock around one's ankle."
3. "If one is *taking out the garbage*, then one must tie a small piece of red volcanic rock around one's ankle."

The italic portion of these permission rules specifies an action that one is permitted to take only if a requirement is met (the red rock is worn). What varies is whether this action is a benefit to the potential violator. Our subjects were undergraduates, for whom going out at night (rule 1) is a highly favored activity. Staying home at night (rule 2) is usually neutral: it is what you do when you have too much work, do not have a date, etc. Taking out garbage (rule 3) is a mildly unpleasant chore.

From the standpoint of permission schema theory, there is no theoretical difference between rules 1–3. Permission rules regulate when an action can be taken—whether that action benefits the potential violator or not. Cheng and Holyoak (1989) are very clear on this point; indeed, it is the basis for their claim that high performance on precautionary rules (where the action taken is hazardous and unpleasant) supports the existence of a permission schema. If permission schema theory is correct, all three rules will elicit high levels of violation detection, resulting in equally high percentages of *P & not-Q* responses.

Benefits play no role in permission schema theory, but they play a key role in social contract theory. Because rule 1 regulates access to an activity that our subjects recognize as a benefit, it should be interpreted as a social contract. This should activate the cheater detection mechanism, leading to a high level of *P & not-Q* responses. In contrast, rules 2 and 3 do not regulate access to a benefit. Lacking this key element, they are less likely to be interpreted as social contracts, and less likely to activate cheater detection. For this reason, social contract theory predicts that rules 2 and 3 will yield a significantly lower percentage of *P & not-Q* responses than rule 1.

That is precisely what happened. Rule 1—the social contract—elicited the correct response (*P & not-Q*) from 80% of subjects (20/25). Only 52% of subjects (13/25) answered correctly for rule 2, and 44% (11/25) for rule 3. Both of these percentages are significantly lower than that found for the social contract (80% vs. 52%: $Z = 2.09$, $P = 0.018$, $\Phi = 0.30$; 80% vs. 44%: $Z = 2.62$, $P = 0.0044$, $\Phi = 0.37$). Rules 1 and 2 are true minimal pairs: They differ by only two words (going out vs. staying home)—a trivial difference of no importance for permission schema theory. Yet this two-word difference, which affects whether the antecedent is a benefit or not, caused a drop in performance of 26 percentage points. The garbage problem was included because the less pleasant the activity being regulated, the lower the probability that subjects will interpret the rule as a social contract; this predicts a monotonic decrease in performance from going out to staying home to garbage. Contrast analysis confirms this (several monotonically decreasing models work, with $\lambda = +3, -1, -2$ providing the best fit, $Z = 3.06$, $P = 0.0011$; see also note 1 of SI Text).

Note that rule 3, the garbage rule, is *capable* of eliciting high levels of violation detection. In a parallel study, 72% of subjects (18/25) answered

correctly when the garbage rule was embedded in a story indicating that the people of this tribe view it as precautionary—that is, when taking out the garbage involves hazards that can be avoided by wearing the rock [72% (precautionary) vs. 44% (not precautionary): $Z = 2.01$, $P = 0.02$, $\Phi = 0.28$; see experiment 5 of supporting information (SI Text)]. This illustrates an important point: High levels of violation detection are typically found for social contracts and for precautionary rules, but not for permission rules that fall outside these categories. The garbage and staying home problems in experiment 1 elicited poorer performance because they were not social contracts *or* precautionary.

What about the requirement term? A rule is a social contract if it regulates access to a benefit; it does not matter whether the requirement the individual must satisfy to be entitled to that benefit is personally costly, neutral, or even beneficial. The requirement is imposed not because it is costly to the person who must satisfy it, but because doing so creates a situation that the *agent who imposed it* wants to achieve. In a separate study, we confirmed this prediction: Varying whether the requirement is costly or beneficial to the potential violator had no effect on performance (experiment 1-A, SI Text).

**Experiment 2**

Experiment 2 is a conceptual replication of experiment 1, using the 1970s-era Sears problem:

4. "You work as an assistant at Sears. You have the job of checking sales receipts to make sure that any sale over $30 has been approved by the section manager (this is a rule of the store)."

The cards, which have information about four sales receipts, read "$70," "$15," "signed," and "not signed" (SI Text). D'Andrade [in Rumelhart and Norman (1981)] reports performance of ~70% on this problem.

According to Cosmides (1985, 1989), performance on the Sears problem is high because it engages the social contract algorithms. Sears is an institution devoted to social exchange, with policies to prevent cheating—checking credit cards and driver's licenses, asking for phone numbers on checks, and so on. The more expensive the item, the worse it is for the store when people do not pay. Requiring manager approval for expensive items is one way stores protect themselves from potential cheaters: The manager approves the expensive purchase only when there are indications that the customer will be able to pay. The rule therefore regulates access to a benefit: goods worth more than $30 versus those worth less. Others dispute this interpretation, arguing that the Sears problem is a permission rule but not a social contract, and that high performance on this problem

demonstrates the existence of a reasoning mechanism general to the class of deontic rules (Cheng and Holyoak, 1989; Manktelow and Over, 1990).

There is no need to engage in verbal arguments when these two views can be tested empirically by comparing performance on rule 4, the original Sears problem, with closely matching rules that do not regulate access to a benefit. To this end, we created permission rules that are about inventory forms rather than sales receipts, such as:

5. "You work as an assistant at Sears. Each department at Sears (Menswear, Sportswear, Ladies Shoes, etc.) has a different color inventory form to fill out. You have the job of checking inventory forms that the department clerks have filled out to make sure that any blue inventory form has been signed by the section manager. (This is a rule of the store.)" (Cards read: "blue," "white," "signed," "not signed.")

By making the rule about inventory forms, we have created a permission rule that subjects are unlikely to interpret as a rule regulating access to a benefit: It is unclear how anyone might benefit by filling out a blue inventory form rather than a white one. If high performance on rule 4 was caused by social contract algorithms, then performance on rule 5 should be lower. By contrast, a permission schema should generate equally high performance on rules 4 and 5.

Contrary to the predictions of permission schema theory, performance on the Sears inventory problem was significantly lower than performance on the original Sears problem: 72% correct (18/25) on rule 4 versus 48% correct (12/25) on rule 5 ($Z = 1.73$, $P = 0.04$, $\Phi = 0.24$). Can it be pushed even lower by removing elements relevant to social exchange?

Most people know that requiring signatures is a common device to protect against cheating; the fact that a manager's signature is required for blue inventory forms could suggest to some that valuable goods are being tracked by the blue forms, but not the white ones. To remove any hint that *P* might represent access to something more valuable than *not-P*, we created rule 6, an inventory rule that regulates where blue forms are to be filed (SI Text). The first two sentences were the same as for rule 5, but it continued as follows:

6. "Filled out inventory forms are to be filed in various bins. You have the job of checking inventory forms that the department clerks have filled out to make sure that any blue inventory form has been filed in the metal bin. (This is a rule of the store.)" (Cards read: "blue," "white," "metal bin," "wood bin.")

Performance was even lower in response to rule 6: 32% correct (8/25). Yet it is a permission rule set in a culturally familiar context. Consistent with the view that performance should decrease with the removal of cues suggesting a benefit is being regulated, contrast analysis confirms a monotonic decrease from sales receipts (72%) to signed inventory forms (48%) to filed inventory forms (32%) (with $P \leq 0.0012$, $Z \geq 3.04$ for $\lambda = 3, -1, -2$ and $1, 0, -1$).

These results support social contract theory and disconfirm permission schema theory. Indeed, they refute any theory [including Fodor's (2000)] that attributes good violation detection to the entire domain of deontic rules.

Cheater detection has a signature: *Benefit accepted* and *requirement not met* are chosen, regardless of logical category. That the conditional rule regulates access to a benefit is a necessary condition for eliciting the detection of this very precise type of violation (Cosmides, 1989; Fiddick et al., 2000). It is not, however, a sufficient condition (Gigerenzer and Hug, 1992)—a prediction that we test in experiments 3 and 4.

## INTENTIONAL VIOLATIONS VERSUS INNOCENT MISTAKES

Intentionality plays no role in permission schema theory. Whenever the action has been taken but the precondition has not been satisfied, the permission schema should register that a violation has occurred. As a result, people should be good at detecting violations of permission rules, whether the violations occurred by accident or by intention. Other deontic theories make the same prediction, because their explanations rest on how the rule is interpreted, not on properties of the violator.

By contrast, the evolved function of a cheater detection subroutine is to use cues of an intentional failure to meet the requirement to correctly connect an attributed disposition (to cheat) with a person (a cheater), for the reasons outlined above. Accidental violations may result in someone not getting what they are entitled to, but without indicating the presence of a cheater. Social contract theory therefore predicts that the same social contract rule will elicit lower violation detection when the context suggests that violations were occurring by mistake rather than by intention (Cosmides and Tooby, 1989; Gigerenzer and Hug, 1992). One partial test showed lowered violation detection when the individuals who might mistakenly violate the social contract were not in a position to obtain the benefit regulated by it (Fiddick, 2004). However, as the benefits experiments above make clear, this lower performance might have been due to the lack of a benefit to the violator, and not to intentionality at all.

We designed experiments 3 and 4 to clearly test whether intentionality regulates violation detection in social exchanges and, if so, to pinpoint

exactly what cues activate or inactivate social contract algorithms. If the cheater detection mechanism is designed to check whether the potential violator has obtained the benefit specified in the rule, then we would see a drop in performance when the violator will not obtain that benefit—even if his violation was intentional. Another possibility is that the cheater detection mechanism is not activated by innocent mistakes—even when the rule violator gets the benefit regulated by the rule by making this mistake. A third possibility is that the social exchange system is designed to respond to both of these factors.

**Experiment 3: Intentionality Without Benefits**

In this study, the social contract rule was held constant; what varied was whether the potential violators were (*i*) cheaters (individuals who intend to violate the rule to obtain the regulated benefit); (*ii*) saboteurs (individuals who intend to violate the rule, but do so to obtain another benefit, rather than the benefit regulated by the rule); or (*iii*) people who may have made innocent mistakes (no intention to violate, no benefit gained by doing so).

The social contract regulated access to a very high quality school, Dover High. The story explains that it is a great school with an excellent record for placing students in good colleges; the neighboring school, Hanover High, is mediocre, with poor teachers and decrepit facilities. The story further explains that Dover High is good because the people of Dover City pay high taxes to support it; in contrast, the equally prosperous people of Hanover and Belmont (neighboring communities) have not been willing to spend the money it would take to improve Hanover High.

Taking these factors into account, the Board of Education made rule 7:

7. "If a student is to be assigned to Dover High School, then that student must live in Dover City."

In all versions, subjects are asked to imagine that they supervise four volunteers at the Board of Education who are supposed to follow rule 7. Each card represents the documents of one student, and the subject is asked which they need to turn over to see whether the documents of any of these students violate the rule.

In the cheater condition, each volunteer is the mother of a teenager who is about to enter high school, and each processed her own child's documents; the concern is that some might have cheated. In the innocent mistake condition, the volunteers are helpful elderly ladies who have become absent-minded; the concern is that some might have violated

the rule by mistake. In the sabotage condition, the volunteers are mad at you for having fired their best friend; the concern is that they intend to violate the rule, with the goal of creating chaos that will make you look incompetent in the eyes of your boss.

Performance was best in the cheater condition and worst in the innocent mistake condition: 68% versus 27% correct (23/34 vs. 9/33; $P = 0.0005$, $\Phi = 0.40$). The sabotage condition elicited intermediate performance of 45% correct (15/33)—significantly worse than the cheater condition ($P = 0.033$, $\Phi = 0.22$) and marginally better than the innocent mistake condition ($P = 0.06$, $\Phi = 0.19$). Contrast analysis confirms a linear decrease in performance in the cheater, sabotage, and innocent mistake conditions ($\lambda = +1, 0, -1$: $Z = 3.62$, $P = 0.00015$), and performance on all three was significantly better than on two other permission rules tested that were not social contracts at all, one using rule 7 ($10^{-6} < P\text{s} < 0.047$; SI Text).

The results indicate that the cheater detection mechanism is most strongly activated by situations suggesting there are individuals who (*i*) *intend* to violate a social contract rule, and (*ii*) will *gain the benefit* it regulates by doing so. Removing the ability to gain this benefit while retaining the intention to violate decreased performance by ~20 percentage points; removing both factors decreased performance by ~40 percentage points.

Experiment 4 tests this interpretation in a full parametric study. It tests whether the effects of these variables are independent, and whether accidental violations decrease performance even when the violator *will* benefit from her mistake.

### Experiment 4: Manipulating Intentions, Benefits, and Ability

Eight Wason problems were tested, all using the same social contract—a version of rule 7 ("If a student is to be assigned to Grover High School, then that student must live in Grover City"). The story provided the same explanation as before: Grover High is better than Hanover High, and access to this benefit is restricted to students living in the community that pays higher taxes to support it (SI Text).

Everything about the problems was held as constant as possible, while three variables were manipulated: (*i*) whether the volunteers intended to violate the rule (*intention* present vs. absent); (*ii*) whether the volunteers could gain the benefit regulated by the rule by violating it (*benefit* present vs. absent); and (*iii*) whether the *ability* to easily cheat was present or absent. These three variables were fully crossed in a 2 × 2 × 2, between-subjects design.

The search for rule violations is unlikely to reveal individuals with a disposition to cheat when the situation prevents cheating. The *ability* vari-

able was included to see whether cheater detection is relaxed under these circumstances. In real life, some situations preclude cheating (Gigerenzer and Hug, 1992), either by both parties (e.g., simultaneous exchange of goods; working jointly on a shared project) or by one party (e.g., having done a favor in advance of reciprocation precludes cheating by the favor doer). In other situations, measures are taken to make cheating more difficult. To simulate the latter situation, the *ability-absen*t conditions said that students were identified by code numbers so that the volunteers could not know which documents belonged to which child. This information was omitted from the *ability-present* conditions.

As above, *benefit-present* conditions explained that each volunteer is the mother of a teenager who is about to enter high school, and each processed her own child's documents. *Benefit-absent* conditions said none of the four volunteers have children in school and so could not benefit from misassigning students. *Intention present* conditions said you (the supervisor) overheard that some of your volunteers intended to try to break the rules when it came to assigning children to schools (or "mischievously intended," to create a motive for this intention in the *benefit-absent* conditions). *Intention-absent* conditions explained that you believe your volunteers are honest, but suspect they may have made some innocent mistakes and broken the rules for assigning each child to a particular school. The percentage of subjects correctly detecting violations by choosing the Grover High card (*P*), the town of Hanover card (*not-Q*), and no others is shown for each condition in Fig. 15.2.

The results were remarkably clear: Each factor—benefit, intention, and ability—contributed to violation detection, independently and additively (three-way ANOVA, main effects: *Benefit* $F_{1,342} = 7.30$, $P = 0.007$, $\eta = 0.14$; *Intention* $F_{1,342} = 10.22$, $P = 0.002$, $\eta = 0.17$; *Ability* $F_{1,342} = 4.87$, $P = 0.028$, $\eta = 0.12$; no interactions). The percentage of subjects who answered correctly was 64% when all three factors were present (BIA), 46% when only two factors were present (BI, BA, or IA), and 26% when only one factor was present (B, I, or A)—the same performance found when no factors were present. That is, each time a factor was removed, performance dropped by about 20 percentage points. This is the same pattern found in experiment 3, where ability to cheat was always present: 68% correct for the three-factor cheater condition (BIA), 45% correct for the two-factor sabotage condition (IA), and 27% correct for the one-factor innocent mistake condition (A) (SI Text, note 2).

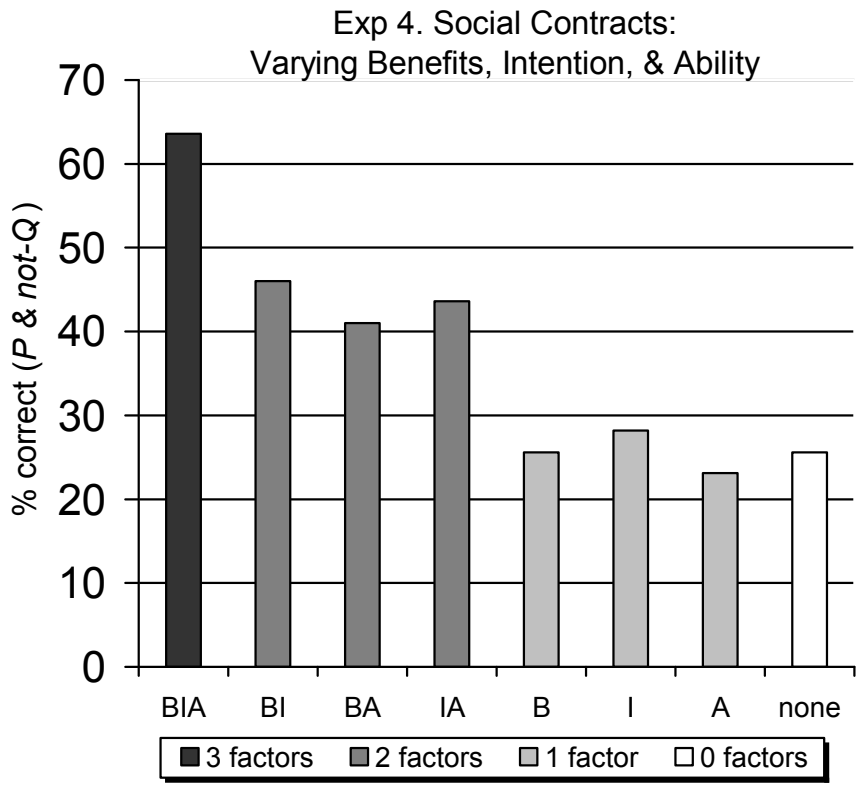


FIGURE 15.2 Parametric study of social contract reasoning. In all conditions, subjects were asked to look for violations of the same social contract. What varied was whether potential violators could *benefit* by violating the rule (B), whether their violating the rule was by *intention* or by mistake (I), and whether the situation provided them with the *ability* to easily violate it (A). When all three factors were present (BIA), performance was highest. It dropped significantly when only two factors were present (BI, BA, IA), and again when only one factor was present (B, I, A)—to the same low level found when none of these factors were present.

## DISCUSSION

### Problems with Deontic and Other Theories

Experiments 1–4 falsify every deontic theory that we are aware of: ones that apply to the entire class of deontic rules, as well as ones that apply only to those involving utilities. Why? If high performance on social contracts were due to the ability to do well on deontic rules, then subjects should routinely do well on problems where the deontic rules are neither

social contracts nor precautions. They do not. In all cases tested in these experiments, subjects did poorly on deontic rules that did not allow the detection of a cheater. This was true even for social contracts, which are deontic permission rules involving utilities: Performance was high when detecting violations would reveal cheaters, but low when it would not.

**Interpretation Theories Ruled Out**

Most theories attempting to explain the spike in violation detection for deontic rules focus on how the rule itself is interpreted. These theories claim that violations are detected because deontic conditionals are interpreted as implying either (*i*) the inferences of a permission schema (Cheng and Holyoak, 1985); (*ii*) the slightly more general (but otherwise identical) inferences of the material conditional in first-order logic (Almor and Sloman, 1996); (*iii*) that cases of *P & not-Q* are forbidden [relevance theory (Sperber et al., 1995)]; or (*iv*) that *Q* is required (Fodor, 2000). None of these theories can explain the results of experiments 1–4 because, although every rule tested was clearly framed as a deontic conditional, most failed to elicit good violation detection.

This is most strikingly demonstrated by the results of experiment 4, where the same social contract, with the same interpretation, was used in every condition. Despite holding the rule and its interpretation constant, we predicted and found systematic decreases in violation detection. This was accomplished by subtracting cues that the search for violations might reveal people with a disposition to cheat. Each cue removed dropped performance by ~20 percentage points, from a high of 64% (three cues) to 46% (two cues) to 26% (one cue).

**Economic and Utility Consequences Ruled Out**

Economics, utility theory, behaviorism, and common sense all lead to the expectation that a lifetime of not getting what you are entitled to would build skill at detecting violations of social contracts. Yet our subjects were not good at detecting these violations unless doing so might reveal a cheater—someone who had intentionally taken the benefit without meeting the requirement.

Some reasoning researchers take a similar tack. To explain why social contracts and precautionary rules—but not other deontic conditionals—elicit good violation detection, they propose that the deontic rule must involve utilities, and that a rule violation must have consequences for someone's utility [e.g., Manktelow and Over (1991); Kirby (1994), Oaksford and Chater (1994) on optimal data selection and decision theory; Sperber et al. (1995) on relevance theory]. However, the results of experiments 3

and 4 cannot be explained by these theories either. The school problem was a social contract and, whether it is violated by accident or intent, in all cases violations will produce an event with consequences for other people's utility: someone's child will get access to a benefit they are not entitled to, and the school board (and taxpayers) will experience a loss—they will incur the expense of providing a benefit to families that did not pay for it (on loss, see Fiddick and Rutherford (2006); SI Text, note 3].

The most dramatic demonstration that "consequences for utility" is an inadequate explanation comes from comparing the four *benefit-present* conditions of experiment 4 (BIA, BI, BA, B; Fig. 15.2). A rule violation has obvious consequences for utility in all of these cases: A volunteer will benefit if her child is assigned to a good school that she did not pay for—a point which is brought to the subject's attention (SI Text, note 2). Yet performance decreased as a function of *intention* and *ability*, from 64% in the BIA condition, to 41% and 46% in the BA (*intention* removed) and BI (*ability* removed) conditions, to 26% in the B condition (*intention* and *ability* removed). Indeed, the relevance [sensu Sperber et al. (1995)] of discovering violations is highest in the BI condition, because this would reveal that the anti-cheating measures taken are ineffective, that people are intentionally breaking the rule despite these measures, and that they are getting an unearned benefit by doing so. Yet performance in this condition was lower than for the BIA condition, and similar to performance in the BA condition, where there was no intention to cheat.

Lastly, the deontic + utility theories cannot explain the results by claiming—post hoc—that violation detection procedures are simply not activated by the prospect of accidents and other innocent mistakes. If this were true, then violation detection should suffer when people are asked to look for accidental violations of precautionary rules; like social contracts, these are deontic conditionals involving utilities. Yet the accident-intention manipulation has no effect whatsoever on precautionary rules: people easily detect accidental violations of them (Fiddick, 2004). This is what one would expect if they were being processed by the precautionary system—an adaptive specialization with a different evolved function.

### The Remarkable Functional Specificity of Cheater Detection Algorithms

Progress is made not only by ruling out rival theories but by mapping additional design features in the architecture of social contract algorithms. These experiments clarify a number of design features of the social contract inferential specialization. Based on the distinctive pattern in which violation detection is up-regulated and down-regulated, we now know that at least three cues independently contribute to cheater detection. First,

intentional violations activate cheater detection, but innocent mistakes do not. Second, violation detection is up-regulated when potential violators would get the benefit regulated by the rule, and down-regulated when they would not. Third, cheater detection is down-regulated when the situation makes cheating difficult—when violations are unlikely, the search for them is unlikely to reveal those with a disposition to cheat. This provides three converging lines of evidence that the mechanism implicated is not designed to look for general rule violators, or deontic rule violators, or violators of social contracts, or even cases in which someone has been cheated; it does not deign to look for violators of social exchange rules in cases of mistake—not even in cases when someone has accidentally benefited by violating a social contract. Instead, this Inspector Javert-like system is monomaniacally focused on looking for social contract rule violations when this is likely to lead to detecting cheaters—defined as agents who obtain a rationed benefit while intentionally not meeting the requirement.

Consider, however, that this system has the computational power to detect social contract violations—it must, to detect cheaters. Yet it is regulated so that violation detection is deployed only in the service of cheater detection. It is difficult to think of a more powerful signal of the system's functional specificity than that.

**Specializations, Modularity, and Intelligence**

Finally, our results prompt a rethinking of the relationship between functional specificity and modular accounts of intelligence. The term *module* was originally borrowed from engineering, to refer to a device specialized to perform a specific function. This meaning dovetails nicely with the concept of an adaptive specialization. Unfortunately, this simple and useful definition became encrusted with additional concepts after the publication of Fodor's book, the *Modularity of Mind*, in which he argued that "information encapsulation" is an important, if not criterial, property of mental modules. This led many cognitive scientists to construe modules as inherently noninteractive, inflexible, reflex-like, and narrow, partitioning information into compartments or pipelines where it is incapable of interacting with other information (Fodor, 1983).

Our results show that the cheater detection system is highly specialized to perform a specific function, which fits the original definition of a module. There is also a very weak sense in which it is informationally encapsulated: to perform its function, it requires representations of interactions among agents that fit the benefit-requirement template of a social contract. But it is nothing like an information pipeline.

In contrast to the Fodorian view, our results show that in monitoring for cheaters, multiple inferential processes are simultaneously brought to bear. It requires a system that infers agent-specific utilities, which itself recruits a number of more specialized systems. To assess the benefits taken and requirements met in social exchanges, this system had to compute the interests of the parties involved—inferring, for example, that processing one's own children's documents implies a potential to benefit through a kin relationship, though this is never explicitly stated. That the cheater detection system responds more strongly to intentional violations than to innocent mistakes implies that it monitors the intentions of the parties involved, suggesting recruitment of specialized inferential mechanisms known as "mindreading" or "theory of mind" (Baron-Cohen, 1995). That it monitors how the ability of subjects to cheat might be constrained by causal properties of the situation, such as access to relevant information, implicates additional processes of causal reasoning. And all of these inferences were applied not to a real situation, but to an imagined one, implying a system that allows suppositional reasoning to occur in a way that is decoupled from semantic memory (Leslie, 1987; Cosmides and Tooby, 2001).

The fact that these processes interact in determining subjects' choices in our tasks suggests that the cheater detection mechanism, despite being a specialized, modular process, does not operate in isolation from other specialized, modular processes such as a kinship psychology, theory of mind, and causal reasoning (Leslie, 1987; Baron-Cohen, 1995; Lieberman et al., 2007). Instead, multiple mechanisms interact synergistically. From a functionalist point of view this should not be surprising, given that cognitive scientists have long held that the adaptive benefit of carving up complex problems into smaller parts is to leverage the synergistic gains afforded by the interaction of specialized processes, much like in an economy (Simon, 1962; Minksy, 1995; Barrett, 2005). However, it clearly falsifies a common but mistaken view of modularity as noninteractivity, a view that has led to widespread but mistaken resistance to modular, adaptationist views of cognition. Contrary to that view, emergent synergies of interacting parts are the hallmark of evolved specialized design. This means that it is likely that no single ability alone, such as cooperation, or theory of mind, or causal reasoning, is likely to explain the unique aspects of human intelligence. Instead, a complete account of human intelligence is likely to require explaining both how multiple cognitive abilities interact, and the novel forms of flexibility that those interactions afford (Barrett et al., 2007).

## CONCLUSIONS

An evolutionary approach to human intelligence leads to the radically different—and highly counterintuitive—view that our cognitive architecture includes evolved reasoning programs that were specialized by selection for distinct adaptive problems, such as social exchange and evading hazards. Although such a view strikes many as implausible in the extreme—why would anything in the mind be so strangely specialized?—the careful analysis of adaptive problems allows the derivation of rich sets of testable and unique predictions about our cognitive architecture. When these predictions are empirically tested—as here—the results typically support the view that the human cognitive architecture contains specializations for adaptive problems our ancestors faced. In this case, we can show that the cheater detection system functions with pinpoint accuracy, remaining inactive not only on rules outside the domain of social exchange but also on social exchanges that show little promise of revealing a cheater. In the contest of intuition versus evidence, it will be interesting to see which will prove the more persuasive. Human intelligence, like the sediments of east Africa, may preserve powerful signals from the evolutionary past. And, maybe, the Earth really does orbit the sun.

## ACKNOWLEDGMENTS

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# 16

# The Difference of Being Human: Morality

FRANCISCO J. AYALA

In *The Descent of Man, and Selection in Relation to Sex*, published in 1871, Charles Darwin wrote: "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." I raise the question of whether morality is biologically or culturally determined. The question of whether the moral sense is biologically determined may refer either to the *capacity* for ethics (i.e., the proclivity to judge human actions as either right or wrong), or to the moral *norms* accepted by human beings for guiding their actions. I propose that the capacity for ethics is a necessary attribute of human nature, whereas moral codes are products of cultural evolution. Humans have a moral sense because their biological makeup determines the presence of three necessary conditions for ethical behavior: (*i*) the ability to anticipate the consequences of one's own actions; (*ii*) the ability to make value judgments; and (*iii*) the ability to choose between alternative courses of action. Ethical behavior came about in evolution not because it is adaptive in itself but as a necessary consequence of man's eminent intellectual abilities, which are an attribute directly promoted by natural selection. That is, morality evolved as an exaptation, not as an adaptation. Moral codes, however, are outcomes of cultural evolution, which accounts for the diversity of cultural norms among populations and for their evolution through time.

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Humans[1] are animals and have evolved from ancestors that were not human. But our "bodily frame," as well as the capacities that stem from it, show also that we are a unique kind of animal, a unique kind of ape, with distinctive features, of which the moral sense is one and, if we are to agree with Darwin, the most important one (Darwin, 1871b, p. 67). As Steven Pinker has written, "Morality is not just any old topic in psychology but close to our conception of the meaning of life. Moral goodness is what gives each of us the sense that we are worthy human beings" (Pinker, 2008, p. 34). In this essay, I will examine morality as a consequential attribute among those that determine "the difference of being human." At issue, of course, stands the evolutionary origin of morality.

## HUMAN UNIQUENESS

Two conspicuous human anatomical traits are erect posture and large brain. We are the only vertebrate species with a bipedal gait and erect posture; birds are bipedal, but their backbone stands horizontal rather than vertical (penguins are a trivial exception) and the bipedalism of kangaroos lacks erect posture and is drastically different from our own. Erect posture and bipedal gait entail other morphological changes in the backbone, hipbone, and feet and others.

Brain size in mammals is generally proportional to body size. Relative to body mass, humans have the largest brain. The chimpanzee brain has an approximate volume of 300 $cm^3$; a gorilla's is slightly larger. The human adult brain is more than three times larger, typically between 1,300 $cm^3$ and 1,400 $cm^3$. The brain is not only larger in humans than in apes but also much more complex. The cerebral cortex, where the higher cognitive functions are processed, is in humans proportionally much greater than the rest of the brain when compared with apes.

Erect posture and large brain are not the only anatomical features that distinguish us from nonhuman primates, even if they may be the most obvious. Other notable anatomical differences include the reduction of the size of the jaws and teeth and the remodeling of the face; reduction of body hair and changes in the skin and skin glands; modification of the vocal tract and larynx, with important implications for spoken language; opposing thumbs that allow precise manipulation of objects; and cryptic ovulation, which may have been associated with the evolution of the nuclear family, consisting of one mother and one father with their children.

Humans are notably different from the apes and all other animals in anatomy, but also and no less importantly in their functional capacities

[1] In this essay, the author draws extensively from Ayala (2010).

and behavior, both as individuals and socially. Most fundamental are the advanced intellectual faculties, which allow humans to categorize (see individual objects as members of general classes), think in the abstract and form images of realities that are not present (and, thus, anticipate future events and planning future actions), and reason. Other distinctive functional features are self-awareness and death awareness; symbolic (creative) language; tool making and technology; complex and extremely variable forms of cooperation and social organization; legal codes and political institutions; science, literature, and art; and ethics and religion (Cela-Conde and Ayala, 2007).

Humans live in groups that are socially organized, and so do other primates. But primate societies do not approach the complexity of human social organization. A distinctive human social trait is culture, which may be understood here as the set of non-strictly biological human activities and creations. Culture in this sense includes social and political institutions, ways of doing things, religious and ethical traditions, language, common sense and scientific knowledge, art and literature, technology, and in general all of the creations of the human mind. Culture "is a pool of technological and social innovations that people accumulate to help them live their lives" (Pinker, 2002, p. 65). The advent of culture has brought with it cultural evolution, a superorganic mode of evolution superimposed on the organic mode, which has, in the last few millennia, become the dominant mode of human evolution. Cultural evolution has come about because of cultural change and inheritance, a distinctively human mode of achieving adaptation to the environment and transmitting it through the generations (Cela-Conde and Ayala, 2007; Varki et al., 2008; Cosmides et al., Chapter 15, this volume; Deacon, Chapter 14, this volume; Pinker, Chapter 13, this volume; Richerson et al., Chapter 12, this volume).

## MORAL BEHAVIOR

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 similar definition is advanced, for example, 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" (Mish, 1998). Altruism, however, is usually taken to imply some cost to the altruist for the benefit of others, and this is the sense in which I will use "altruism" here. Moreover, "altruism" is often predicated on the

behavior of social insects and other animals, in which no intentionality is involved but rather comes about as a result of genetically determined behaviors. This is biological altruism, or altruism$_b$, in contrast to moral altruism, or altruism$_m$ (Ayala, 1987).

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 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 or eating pork, will not be included either in my use of "morality," so long as the actions have no consequences for others.

## THEORIES OF MORALITY

People have moral values; that is, they accept standards according to which their conduct is judged as either right or wrong, 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, such as 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 two related questions: whether the moral sense is part of human nature, one more dimension of our biological makeup; and whether ethical values may be products of biological evolution rather than being given by religious and other cultural traditions.

When philosophers consider theories of morality they distinguish between metaethics, normative ethics, and practical ethics (Copp, 2006). Theories of metaethics seek to justify why we ought to do what we ought to do. They are the primary concern of philosophers, who favor different theories, such as "divine command" (God's commanding is what makes a particular kind of action moral); "moral realism" (there are moral facts; our moral judgments are made valid or not by the moral facts); "utilitarianism" (the moral value of an action is determined by the expected benefit to the largest number of people); "positivism" (there are no objective rational foundations for morality, but rather moral norms are determined by social agreement or, in the individual, by emotional decisions); "libertarianism" (moral values are measured by the extent to which they maximize per-

sonal freedom and limit the role of the state to the protection of individual freedoms); and several others.

Normative ethics refers to the rules or laws that determine what we ought to do. Practical ethics considers the application of moral norms to particular situations, which often involve conflicting values: will abortion be justified to save the life of the mother?

In practice, humans justify the set of moral norms they follow on several, not only one, metaethical doctrines. Thomas Aquinas, the 13th century Christian theologian whose authority is highly respected up to the present, says that some moral laws come from divine authority (worship only one God), others from natural law (do not kill, do not commit adultery), and still others from civil authority (respect private property, pay taxes).

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.* For the last 20 centuries, the foundations of morality were an important subject for Christian theologians, as in the case of Thomas Aquinas, but also for philosophers, such as, in the 18th and 19th centuries, Hume, Kant, and others familiar to Darwin, including notably William Paley *(The Principles of Moral and Political Philosophy,* 1785) (Fig. 16.1) and Harriet Martineau *(Illustrations of Political Economy,* 1832–1834).

The theory of evolution brought about the need to reconsider the foundations of morality. 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. Is the moral sense determined by biological evolution? If so, 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 byproduct of some other attribute (such as rationality, for example) 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

Darwin's most sustained discussion of morality is in chapter III of *The Descent of Man* (1871b, pp. 67–102). The keystone significance of morality in human distinctness is clearly asserted by Darwin in the first sentence, already quoted, of chapter III: "I fully subscribe to the judgment of those writers who maintain that of all the differences between man

FIGURE 16.1 William Paley (1743–1805). English theologian who taught at the University of Cambridge, United Kingdom, and author of *The Principles of Moral and Political Philosophy* (1785). His best-known work is *Natural Theology, or Evidences of the Existence and Attributes of the Deity* (1802). Image source: www.nndb.com/people/526/000096238/.

and the lower animals the moral sense or conscience is by far the most important" (1871b, p. 67). Darwin (Fig. 16.2) had started gathering the contemporary literature on human moral behavior much before the publication of *The Descent of Man* in 1871 (Fig. 16.3); indeed, we know from his notebooks that Darwin was reading the contemporary philosophical literature about moral behavior in 1837, only a few years after returning from his trip on the *HMS Beagle* (1826–1831). Treatises that he read early on include the aforementioned *Moral and Political Philosophy* by Paley (1785), which he had already encountered while a student at Cambridge University, and the multivolume *Illustrations of Political Economy* by Harriet Martineau, published more recently, 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, on the grounds of an argument often advanced nowadays by philosophers and anthropologists: the diversity of moral codes.

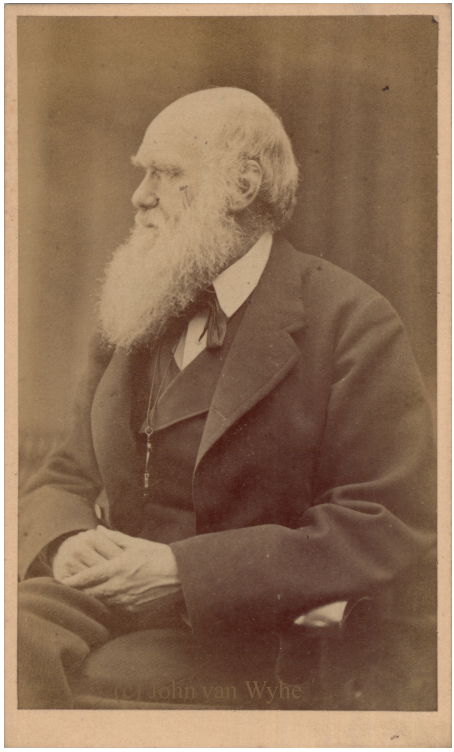
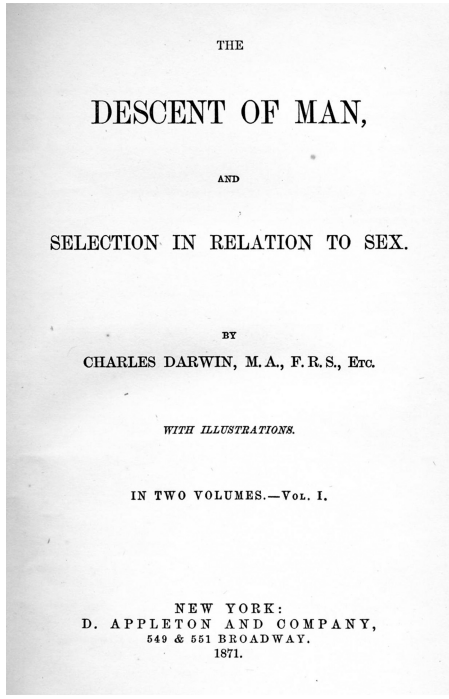



FIGURE 16.2 Charles Robert Darwin (1809–1882). Photograph by Oscar Gustave Rejlander, *ca.* 1871, the year Darwin published *The Descent of Man.* Image source: http://commons.wikimedia.org/wiki/File:Charles_Darwin_photograph_by_Oscar_Rejlander,_ci rca_1871.jpg.

The proliferation of ethnographic voyages had brought to light the great variety of moral customs and rules. This diversity is something Darwin had noticed when comparing the prevailing English and European norms of morality with those of South American Indians and other native populations elsewhere. But Darwin would eventually develop a more complex and subtle theory of the moral sense than his 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.



THE

DESCENT OF MAN,

AND

SELECTION IN RELATION TO SEX.

BY

CHARLES DARWIN, M. A., F. R. S., ETC.

*WITH ILLUSTRATIONS.*

IN TWO VOLUMES.—VOL. I.

NEW YORK:
D. APPLETON AND COMPANY,
549 & 551 BROADWAY.
1871.

FIGURE 16.3 Cover page of Darwin's *The Descent of Man and Selection in Relation to Sex,* first American edition, published by Appleton and Company, New York, in 1871, the same year in which his first English edition was published by John Murray, London.

A variable adaptive response could very well derive from some fundamental attribute, 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 two most significant points concerning the evolution of morality are stated early in chapter III of *The Descent of Man.* The two points are (*i*) that moral behavior is a necessary attribute of advanced intelligence as it occurs in humans, and thus that moral behavior is biologically determined; and (*ii*) that the norms of morality are not biologically determined but are rather a result of human collective experience, or human culture as we would now call it.

After the two initial paragraphs of chapter III of *The Descent of Man,* which assert that the moral sense is the most important difference "between man and the lower animals" (see quotation above), 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" (Darwin, 1871b, 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.

In the ensuing paragraph of chapter III, before proceeding to a discussion of how morality might evolve, Darwin makes an important distinction: "It may be well first to premise that 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 exactly 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" (1871b, p. 70). 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 and which ones would be condemned.

Darwin's distinction between the moral sense or conscience on the one hand, and the moral norms that guide the moral sense or conscience on the other, is fundamental. It is a distinction I will now elaborate. Much of the post-Darwin 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 that distinction. Scientists often affirm that morality is a human biological attribute because they are thinking of the predisposition to make moral judgments, that is, to judge some actions as good and others as evil. Some 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.

## MORAL JUDGMENT VS. MORAL NORMS

The question of whether ethical behavior is biologically determined may, indeed, 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 of whether the capacity for symbolic creative language is determined by our biological nature is different from the question of whether the particular language we speak—English, Spanish, Chinese, etc.—is biologically determined, which in the case of language obviously it is not.

I 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 argue 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, such as parental care to give an obvious example.

## MORAL BEHAVIOR AS RATIONAL BEHAVIOR

The moral sense refers first and foremost to our predisposition to evaluate some actions as virtuous, or morally good, and others as evil, or morally bad. Morality, thus, consists of 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 (*i*) the ability to anticipate the consequences of one's own actions; (*ii*) the ability to make value judgments; and (*iii*) the ability to choose between alternative courses of action. These abilities exist as a consequence of the eminent intellectual capacity of human beings.

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 use of objects for hunting and other activities that improved survival and reproduction, that is, which increased the reproductive fitness of their carriers. 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 improvement 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 diverse and remote purposes. According to the hypothesis, 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 advance 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 apparently in them alone.

I will note at this point that the model that I am advancing here does not necessarily imply the ethical theory known as utilitarianism (or, more generally, consequentialism). According to the so-called "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 (*i*) to anticipate the consequences of our actions, and (*ii*) to make value judgments. 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 and the process of food digestion are not moral actions. Whether there is free will is a question much discussed by philosophers, and the arguments are long and involved [e.g., Kane (1996), Bok (1998), Ekstrom (2000), Fischer (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 (Fig. 16.4).

## ADAPTATION VS. EXAPTATION

I will now consider explicitly two issues that are largely implicit in the previous section. The moral sense, as I have proposed, emerges as a necessary implication of our high intellectual powers, which allow us to anticipate the consequences of our actions, to evaluate such consequences, and to choose accordingly how to act. 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

FIGURE 16.4 Theodosius Dobzhansky (1900–1975), a principal author of the modern theory of evolution. The *In the Light of Evolution* (ILE) Sackler colloquium series is named after Dobzhansky's well-known statement, "Nothing in biology makes sense except in the light of evolution."

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 function but are later co-opted to serve an additional or 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 it is simply a consequence of our exalted intelligence, which was the target of natural selection (because it made possible the construction of better tools). Art, literature, religion, and many human cultural activities might also be seen as exaptations that came about as consequences of the evolution of high intelligence.

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 will 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. It seems unlikely that making moral judgments would promote the reproductive fitness of those judging an action as good or evil; *acting* in one way or another might be of consequence in promoting fitness, but passing *judgment* by itself would seem unlikely to increase or decrease adaptive fitness. 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, which happened mostly through the Pleistocene, of advanced intellectual capacities. This was favored by natural selection because the construction and use of tools, made possible by advanced intelligence, 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 practiced, 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.*

A related question is whether morality would benefit a social group within which it is practiced and, indirectly, would also benefit individuals who are 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. That is, the moral sense that had evolved as an exaptation associated with high intelligence could eventually become an adaptation, by favoring beneficial behaviors.

## GROUP SELECTION IN HUMAN POPULATIONS

I have asserted that patterns of actions beneficial to the tribe or social group might, in humans, be favored by natural selection. This brings up the issue known as "group selection." Evolutionists generally contend that group selection based on altruistic behavior is not an evolutionarily stable

strategy. Altruistic behavior within an animal population would benefit the population itself, so that a population consisting of altruists would do better than a population consisting of selfish individuals. This would be group selection: the population as a whole benefits from the behavior of its individuals. But this state of affairs is not evolutionarily stable in an animal population. The reason is that mutations that favor selfish over altruistic behavior will be favored by natural selection, because the behavior of an altruistic individual implies a cost. The altruistic individual as well as the rest of the population will benefit from the behavior of the altruist. A selfish individual also benefits from the behavior of the altruist, but the selfish individual does not incur the cost implied by the altruistic behavior. Thus, selfish behavior will be favored within the population. Natural selection will thus eliminate genetically determined altruistic behaviors.

Of course, it is admitted that it might be the case that populations with a preponderance of altruistic alleles would 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 in a given population 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 necessarily apply to humans, because humans can *understand* the benefits of altruistic behavior (it benefits the group but indirectly it benefits them as well) 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" (1871b, chap. V, p. 159).

The theory of sociobiology advances a ready answer to the second question raised above, whether morality occurs in other animals, even if only as a rudiment. The theory of kin selection, they 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 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. Biological altruism ($altruism_b$) and moral altruism ($altruism_m$) have disparate causes: kin selection in $altruism_b$, regard for others in $altruism_m$.

## MIND TO MORALITY

The capacity for ethics is an outcome of gradual evolution, but it is an attribute that only exists when the underlying attributes (i.e., 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 occur in the physical world as well; 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.

Yet, 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.

A different explanation of the evolution of the moral sense has been advanced by proponents of the theory of "gene–culture coevolution" (Simon, 1990; Richerson and Boyd, 2005; Haidt, 2007; Strimling et al., 2009; Richerson et al., Chapter 12, this volume). 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 whereby 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 am advancing here, 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 would seem to favor the explanation I am proposing. Gene–culture coevolution would rather lead to a more nearly universal system of morality, which would have come about gradually as our hominid 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, 2008, chap. 5, pp. 158–199). Empathy is a common human phenomenon, surely associated with our advanced intelligence, which allows us to understand the harms or benefits that impact 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 then 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, *Homo neanderthalensis*? When in hominid evolution morality emerged is difficult to determine. It may very well be that 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 discussed in Cela-Conde and Ayala (2007).

## MORAL CODES

I have distinguished between moral behavior (judging some actions as good, others as evil) and moral codes (the precepts or norms according to which actions are judged). 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 argue, are not products of biological evolution but rather of cultural evolution.

It must, first, be stated that moral codes, like any other cultural systems, cannot survive for long if they prevailingly run in outright conflict with our biology. The norms of morality must be by and large consistent with human 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 often, or at least occasionally, 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.

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 also horizontally and 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.

In chapter V of *The Descent of Man,* entitled, "On the Development of the Intellectual and Moral Faculties During Primeval and Civilized Times," Darwin 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.
>
> Darwin (1871b, pp. 159–160)

Darwin is making two important assertions. First, that morality may contribute to the success of some tribes over others, which is natural selection in the form of group selection. Second, Darwin is asserting a position of moral optimism, namely that the standards of morality will tend to improve over human history precisely on grounds of group selection, because the higher the moral 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.

## MORAL NORMS AND NATURAL SELECTION

Parental care is a behavior generally favored by natural selection that may 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 sanctioned in some current human cultures and was more so in the past. Food sharing outside the mother-offspring unit rarely occurs in primates, with the exception of chimpanzees—and, apparently, in capuchin monkeys (de Waal, 1996; Brosnan and de Waal, 2003)—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 (de Waal, 1996; Brosnan and de Waal, 2003) 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, because similar behavioral patterns have not been observed in other primates, including apes, phylogenetically closer to humans. 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.

The interpretation of the capuchin monkeys' behavior as an incipient sense of justice (Brosnan and de Waal, 2003) has been challenged by other investigators. Silberberg and collaborators (2009) have shown that the capuchins rejected a reward whenever a more desirable reward was visible to them, not just whenever the more desirable reward was offered to other individuals.

Schiff and de Waal (2005) observed also that chimpanzees rejected a reward when they observed another chimpanzee obtaining a more attractive reward for equal exchange with the human experimenter, although the tolerance for inequity increased with the social closeness among the chimpanzees. However, this interpretation of inequality rejection has also been challenged in the case of the chimpanzees. The chimpanzees' rejection may be attributed to a breach in their expectations, rather than to a sense of equality (Bräuer et al., 2006; Jensen et al., 2007).

Moral codes arise in human societies by cultural evolution. Those moral codes tend to be widespread that lead to successful societies. Since time immemorial, human societies have experimented with moral systems. Some have succeeded and spread widely throughout 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 exist in humankind are those that have been 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 (Gazzaniga, 2005, 2008). Cultures, of course, do not evolve as completely differentiated units. Rather, cultures often incorporate elements from other cultures. "Far from being self-preserving monoliths, cultures are porous and constantly in flux. Language . . . is a clear example" (Pinker, 2002, p. 66).

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, 2008, p. 34). Acceptance by individuals or groups of particular sets of moral norms is often reinforced by civil authority (e.g., those who kill or commit adultery will be pun-

ished) 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 (Ayala, 2010).

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