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12 Human Evolution

The Three Grand Challenges of Human Biology

> Man is but a reed, the weakest in nature, but he is a thinking reed.
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> Blaise Pascal, *Pensées*, number 347

A SUMMARY OF THE ARGUMENT

Human biology faces three great research frontiers: ontogenetic decoding, the brain-mind puzzle, and the ape-to-human transformation. By ontogenetic decoding, or the egg-to-adult transformation, I refer to the problem of how the unidimensional genetic information encoded in the DNA of a single cell becomes transformed into a four-dimensional being, the individual that grows, matures, and dies. Cancer, disease, and aging are epiphenomena of ontogenetic decoding. By the brain-mind puzzle I refer to the interdependent questions of (1) how the physicochemical signals that reach our sense organs become transformed into perceptions, feelings, ideas, critical arguments, aesthetic emotions, and ethical values; and (2) how, out of this diversity of experiences, there emerges a unitary reality, the mind or self. Free will and language, social and political institutions, technology and art, are all epiphenomena of the human mind. By the ape-to-human transformation I refer to the mystery of how a particular ape lineage became a hominid lineage, from which emerged, over only a few million years, humans able to think and love, to develop complex societies and subject to ethical, aesthetic and other values. The human genome differs little from the chimp genome.

The egg-to-adult transformation is essentially similar, and similarly mysterious, in humans and other mammals. The brain-to-mind transformation and the ape-to-human transformation are distinctively human; they define the *humanum*, that which makes us specifically human. No other issues in human evolution are of greater consequence for understanding ourselves and our place in nature.

Erect posture and large brain are two of the most significant anatomical traits that distinguish us from nonhuman primates. But humans are also different from chimpanzees and other animals, and no less importantly, in their behavior, both as individuals and socially. Distinctive human behavioral attributes include tool making and technology; abstract thinking, categorizing, and reasoning; symbolic (creative) language; self-awareness and death awareness; science, literature, and art; legal codes, ethics, and religion; complex social organization and political institutions. These traits may all be said to be components of human culture, a distinctively human mode of adaptation to the environment that is far more versatile and successful than the biological mode.

Cultural adaptation is more effective than biological adaptation because (1) its innovations are directed, rather than random mutations; (2) it can be transmitted "horizontally," rather than only "vertically," to descendants; and (3) because cultural heredity is Lamarckian, rather than Mendelian, acquired characteristics can be inherited.

LIFE TO HUMAN

The oldest known fossil remains of living organisms are dated somewhat earlier than 3,500 million years ago, just a few hundred million years after the Earth had cooled. The organisms were microscopic, individual cells, but having already considerable complexity of organization and elaborate biochemical machinery to carry on the functions of life. We do not know when life started, but it likely was at least one hundred million years earlier.

There are several hypotheses about how life first started, but none of these hypotheses is sufficiently well supported by evidence and, thus, none of them is accepted by all scientists. But the fact that it took "only" one or a few hundred million years from the formation of the Earth to the appearance of the first single-cell organisms, suggests that life in some form is likely to appear in any planet that

has water and a few other elements (notably, in our planet, carbon, nitrogen, phosphorus, and sulfur). The temperature must also be ''right'', within a certain range, as it is the case for planet Earth, because of the 150 million kilometers that separate it from the Sun, so that water can exist in liquid phase (rather than only as either ice or vapor, if the temperature is too low or too high).

There are three large groups of organisms on Earth: eucaryotes, bacteria, and archaea. The eucaryotes include animals, plants, and fungi. Eucaryotes are organisms that have their genetic material enclosed in a special capsule, or organelle, called the nucleus. Humans are eucaryotes. Animals, plants, and fungi are the only organisms that we can directly experience with our senses, and thus they were the only organisms whose existence was known to humans up to three centuries ago. Yet they account for only a fraction of the total diversity of the eucaryotes. The other eucaryotes are all microscopic. Some cause well-known diseases, such as *Plasmodium*, which causes malaria, or *Entamoeba*, which causes severe intestinal maladies.

A second group of organisms are the bacteria. Humans have known of the existence of bacteria for more than a century. We associate them with diseases, but bacteria perform many useful functions, including the incorporation of nitrogen from the atmosphere, nitrogen that animals and plants need but are not able to get directly from the atmosphere (where it is very abundant, about 75 percent of the total; the rest is mostly oxygen). Also, bacteria are responsible for the decomposition of dead matter, a process that is essential in the maintenance of the cycle of life and death, because it makes again available, for new organisms, valuable components that had been incorporated into the now dead organisms. The genetic diversity and number of species of bacteria are at least as large as in the eucaryotes. There are many more kinds of bacteria than there are kinds of animals, plants, and fungi combined. And they are so abundant that their total weight (their ''biomass'') is at least as great as (and probably much greater than) that of all plants, fungi, and animals combined, even though individually they are so much smaller. This is a humbling thought. We see ourselves, the human species, as the summit of life and we are the most numerous of all large animals; and we see animals and plants as the dominant forms of life on Earth. However, modern biology teaches as that, numerically as well as in biomass, the nearly two million known species of animals (including humans) amount only to a very small

fraction of life on Earth. From the perspective of numbers and biomass, the bacteria alone count much more than we do.

There is another group, the archaea, likely to be about as large as the eucaryotes or the bacteria. The existence of the archaea is a very recent discovery of molecular (modern) biology. Because these organisms do not directly interact much with us, biologists were not aware of their existence. Three decades ago scientists only knew a few species, such as those that exist in the hot springs of Yellowstone National Park in the United States and in other volcanic hot springs, where they thrive at temperatures approaching the boiling point of water. Biologists thought that these were some unusual forms of bacteria. Now we know them to belong to a very diverse and numerous group of organisms, abundant in the top water layers of the seas and oceans. A bucket of sea water studied with the modern techniques of molecular biology may yield tens or hundreds of new archaea species.

The number of living species on Earth is estimated to be between 10 and 30 million, but some biologists think that there may be as many as 100 million species, if bacteria and archeaea are included. Animals represent a small fraction of all species now living. More than 99 percent of all animal species that lived in the past have become extinct without issue. This is most likely true for all other kinds of organisms as well. Thus, the total number of species that have existed since the beginning of the Earth is more than one billion. We humans are but one of them.

Humans are animals, but a very distinct and unique kind of animal. Our anatomical differences include bipedal gait and an enormous brain. But we are notably different also, and more importantly, in our individual and social behaviors, and in the products of those behaviors. With the advent of humankind, biological evolution transcended itself and ushered in cultural evolution, a more rapid and effective mode of evolution than the biological mode. Products of cultural evolution include science and technology; complex social and political institutions; religious and ethical traditions; language, literature, and art; radio and electronic communication.

HUMAN ORIGINS

Our closest biological relatives are the chimpanzees, who are more closely related to us than they are to the gorillas, and much more

than to the orangutans. (The chimpanzees include two species closely related to one another, but both equally related to humans, *Pan troglodytes*, or common chimpanzee, and *Pan paniscus*, or bonobo.) The hominid lineage diverged from the chimpanzee lineage 7–8 million years ago (mya) and it evolved exclusively in the African continent until the emergence of *Homo erectus*, somewhat before 1.8 mya (Cela-Conde and Ayala 2001). The first known hominids are the recently discovered *Sahelanthropus tchadensis* (dated 6–7 mya; Brunet et al. 2002; Vignaud et al. 2002), *Orrorin tugenensis* (dated 5.8–6.1 mya; Senut et al. 2001), and *Ardipithecus ramidus* (dated 5.2–5.8 mya; Haile-Selassie 2001). They were bipedal when on the ground, but retained tree-climbing abilities. It is not certain that they all are in the direct line of descent to modern humans, *Homo sapiens*; rather, some may represent side branches of the hominid lineage, after its divergence from the chimpanzee lineage. *Australopithecus anamensis*, dated 3.9–4.2 mya, was habitually bipedal and has been placed in the line of descent to *Australopithecus afarensis, Homo habilis*, *H. erectus*, and *H. sapiens*. Other hominids, not in the direct line of descent to modern humans, are *Australopithecus africanus*, *Paranthropus aethiopicus*, *P. boisei*, and *P. robustus*, who lived in Africa at various times between 3 and 1 mya, a period when three or four hominid species lived contemporaneously in the African continent (see Cela-Conde and Ayala 2001 for an extensive review of hominid evolution).

The first intercontinental wanderer among our ancestors was *H. erectus*. Shortly after its emergence in tropical or subtropical eastern Africa, *H. erectus* dispersed to other continents of the Old World. Fossil remains of *H. erectus* are known from Africa, Indonesia (Java), China, the Middle East, and Europe. *H. erectus* fossils from Java have been dated 1.81 ± 0.04 and 1.66 ± 0.04 mya, and from Georgia between 1.6 and 1.8 mya. Anatomically distinctive *H. erectus* fossils have been found in Spain and in Italy, deposited about 800,000 years ago, the oldest known in Western Europe.

Fossil remains of Neanderthal hominids (*Homo neanderthalensis*), with brains as large as those of *H. sapiens*, appeared in Europe around 200,000 years ago (200 kya) and persisted until 40 kya. The Neanderthals were thought to be ancestral to anatomically modern humans, but now we know that modern humans appeared at least 100 kya, much before the disappearance of the Neanderthals.

Moreover, in caves in the Middle East, fossils of modern humans have been found dated nearly 100 kya, as well as Neanderthals dated at 60 and 70 kya, followed again by modern humans dated at 40 kya. It is unclear whether the two forms repeatedly replaced one another by migration from other regions, or whether they coexisted in the same areas. Recent genetic evidence indicates that interbreeding between *H. sapiens* and *H. neanderthalensis* never occurred.

The origin of anatomically modern humans is controversial. Some anthropologists argue that the transition from *H. erectus* to archaic *H. sapiens* and later to anatomically modern humans occurred consonantly in various parts of the Old World. Proponents of this "multiregional model" call attention to fossil regional continuity in the transition from *H. erectus* to archaic and then modern *H. sapiens*. They postulate that genetic exchange occurred from time to time between geographically separate populations, so that the species evolved as a single gene pool, even though geographic differentiation occurred and persisted, just as geographically differentiated populations exist in other animal species and in modern humans. This claim of interbreeding between *H. erectus* populations depends on the postulate of persistent migrations and interbreeding between distant populations, even from different continents, of which no direct evidence exists, although it is not theoretically unlikely to have occurred. However, it is difficult to conciliate the multiregional model with fossil evidence of the contemporary coexistence of different species (*H. erectus* and *H. sapiens*) or forms (archaic and modern *H. sapiens*) in China, Indonesia, and other regions.

Other scientists argue instead that modern humans first arose in Africa between 150 kya and 100 kya, and from there spread throughout the world, replacing elsewhere the preexisting populations of *H. erectus* or archaic *H. sapiens*. This is called the "Out of Africa" hypothesis, which is now favored by most evolutionists. Genetic and molecular evidence shows greater difference between African and non-African populations than between all non-African human populations. This pattern of differentiation endorses the hypothesis that the origin of anatomically modern humans was in Africa, whence modern humans expanded to the rest of the world, starting about 100 kya. It is not possible, however, to exclude completely a partial participation of archaic *H. sapiens* from the Old

World in the origin of modern humans. Some observations evince the persistence of older anatomical traits in modern human populations of Central Europe and traces of ancient mitochondrial DNA have been found in Australian populations (Wolpoff et al. 2001, Adcock et al. 2001). In any case, genetic analysis supports the occurrence of at least two, not just one, major migrations out of Africa, well after the original range expansion of *H. erectus* (Templeton 2002).

I wrote earlier that *Homo sapiens*, our species, is only one of more than one thousand million species that have lived on Earth since the beginning. From that perspective, humans are but a speck on our planet. This is also the case from the perspective of time. The hominids diverged from the apes about 7–8 mya, and modern humans come into existence about 100 kya. Yet, life has existed on Earth for more than 3,500 my.

It is difficult to think in millions of years. So let me transform the time line of evolution into a one-year scale, so that life arises in our planet on January 1, at zero hours, and so that it is now midnight on December 31. In this one-year scale, for the first eight months there is only microscopic life; the first animals appear around September 1; they are marine animals. The land is colonized around December 1; the primates originate on December 26; the hominids separate from the chimpanzees on December 31, at noon; and modern humans arise on that last day of the year at twenty-three hours forty-five minutes. We have been around for a total of fifteen minutes. That also is a humbling thought. But I hasten to add that even though we are ''but a reed,'' as Pascal famously put it, we are a *thinking* reed, and to this I shall presently return.

THE HUMAN GENOME SEQUENCE

Biological heredity is based on the transmission of genetic information from parents to offspring, in humans very much the same as in other animals. The genetic information is encoded in the linear sequence of the DNA's four nucleotide components (the ''letters'' of the genetic alphabet, represented by A, C, G, T) in a similar fashion to encoding of semantic information in the sequence of letters of a written text. The DNA is compactly packaged in the chromosomes inside the nucleus of each cell. Humans have two sets of twenty-three chromosomes, having received one set from each

parent. The total number of DNA letters in each set of chromosomes is about three thousand million. The Human Genome Project, which was undertaken in 1989, has deciphered the sequence (except for a number of small segments) of the three thousand million letters in the human genome (that is, in one set of chromosomes; the human genome sequence varies among individuals).

I estimate that the King James Bible contains fewer than three million letters, punctuation marks, and spaces. Writing down the DNA sequence of one human genome demands one thousand volumes of the size of the Bible. The human genome sequence is, of course, not printed in books, but stored in electronic form, in computers where fragments of information can be retrieved by investigators. But if a printout is wanted, one thousand volumes will be needed just for one human genome.

The two genomes (chromosome sets) of each individual are different from one another, and from the genomes of any other human being (with the trivial exception of identical twins, who share the same two sets, since identical twins develop from one single fertilized human egg). Therefore, printing the complete genome information for just one individual would demand two thousand volumes, one thousand for each of the two chromosome sets. Surely, again, there are more economic ways of presenting the information in the second set than listing the complete letter sequence; for example, by indicating the position of each variant letter in the second set relative to the first set. The number of variant letters between one individual's two sets is about ten million, about one in three hundred.

The Human Genome Project of the United States was initiated in 1989, funded through two agencies, the National Institutes of Health (NIH) and the Department of Energy (DOE). (A private enterprise, Celera Genomics, started in the United States somewhat later but joined the government-sponsored project in achieving, largely independently, similar results.) The goal set was to obtain the complete sequence of one human genome in fifteen years at an approximate cost of three thousand million dollars, coincidentally about one dollar per DNA letter. A draft of the genome sequence was completed ahead of schedule in 2001. In 2003 the Human Genome Project was finished. The sequence has become known with as much precision as wanted.

Proponents of the project had used inflated rhetoric to extol its anticipated achievements. The project was called the ''Holy Grail'' of biology, which would meet the biblical ''Know thyself'' injunction. The Nobelist Walter Gilbert said about a computer disk encoding an individual's DNA sequence information, ''this is you''.[1] (The Nobelist and first director of the project, James Watson, asserted that ''our fate is in our genes''.)[2] Daniel Koshland, editor at the time of *Science*, proclaimed that with knowledge of the genome sequence, ''we may be able to prevent the damage'' caused by violent behavior.[3] Has the Human Genome Project accomplished any of these lofty objectives? Has knowledge of the human genome sequence accomplished the anticipated promise of curing human diseases?

THREE FRONTIERS OF HUMAN BIOLOGY: BEYOND THE HUMAN GENOME

Human biology faces three great research frontiers: ontogenetic decoding, the brain-mind puzzle, and the ape-to-human transformation. This transformation involved the emergence of cultural heredity and cultural evolution, a new and much more effective mode of adaptation to the environment than the biological mode. The conundrum is how this was accomplished through the change of less than 2 percent of the genome.

One can refer to these three issues as the egg-to-adult transformation, the brain-to-mind transformation, and the ape-to-human transformation.

Knowing the DNA sequence of human beings is of great use as a database to biologists and health scientists. But such knowledge about the human genome does not by itself contribute much to the solution of any of the three conundrums I have identified here, or to the solution of any other fundamental biological problem.[4]

ONTOGENETIC DECODING

The instructions that guide the ontogenetic process, or the egg-to-adult transformation, are carried in the hereditary material. The theory of biological heredity was formulated by the Augustinian monk Gregor Mendel in 1866, but it became generally known by

biologists only in 1900: genetic information is contained in discrete factors, or genes, that exist in pairs, one received from each parent. The next step toward understanding the nature of genes was completed during the first quarter of the twentieth century. It was established that genes are parts of the chromosomes, filamentous bodies present in the nucleus of the cell, and that they are linearly arranged along the chromosomes. It took another quarter-century to determine the chemical composition of genes – deoxyribonucleic acid (DNA). DNA consists of four kinds of chemical components (nucleotides) organized in long, double-helical structures. As pointed out earlier, the genetic information is contained in the linear sequence of the nucleotides, very much in the same way as the semantic information of an English sentence is conveyed by the particular sequence of the twenty-six letters of the alphabet.

The first important step toward understanding how the genetic information is decoded occurred in 1941 when George W. Beadle and Edward L. Tatum demonstrated that genes determine the synthesis of enzymes; enzymes are the catalysts that control all chemical reactions in living beings. It became known later that a series of three consecutive nucleotides in a gene codes for one amino acid (amino acids are the components that make up enzymes and other proteins). This relationship accounts for the precise linear correspondence between a particular sequence of coding nucleotides and the sequence of the amino acids that make up the encoded enzyme.

But chemical reactions in organisms must occur in an orderly manner; organisms must have ways of switching any gene on and off. The first control system was discovered in 1961 by François Jacob and Jacques Monod for a gene that determines the synthesis of an enzyme that digests sugar in the bacterium *Escherichia coli*. The gene is turned on and off by a system of several switches consisting of short DNA sequences adjacent to the coding part of the gene. (The coding sequence of a gene is the part that determines the sequence of amino acids in the encoded enzyme.) The switches acting on a given gene are activated or deactivated by feedback loops that involve molecules synthesized by other genes. A variety of gene control mechanisms were soon discovered, in bacteria and other microorganisms. Two elements are typically present: feedback loops and short DNA sequences acting as switches. The feedback loops ensure that the presence of a substance in the cell induces the synthesis of

the enzyme required to digest it, and that an excess of the enzyme in the cell represses its own synthesis. (For example, the gene encoding a sugar-digesting enzyme in *E. coli* is turned on or off by the presence or absence of the sugar to be digested.)

The investigation of gene control mechanisms in mammals (and other complex organisms) became possible in the mid-1970s with the development of recombinant DNA techniques. This technology made it feasible to isolate single genes (and other DNA sequences) and to multiply them, or "clone" them, in order to obtain the quantities necessary for ascertaining their nucleotide sequence. One unanticipated discovery was that most genes occur in pieces: the coding sequence of a gene is divided into several fragments separated one from the next by noncoding DNA segments. In addition to the alternating succession of coding and noncoding segments, mammalian genes contain short control sequences, like those in bacteria but typically more numerous and complex, that act as control switches and signal where the coding sequence begins.

Much remains to be discovered about the control mechanisms of mammalian genes. The daunting speed at which molecular biology is advancing makes it reasonable to anticipate that the main prototypes of mammalian gene control systems will be unraveled within a decade or two. But understanding the control mechanisms of individual genes is but the first major step toward solving the mystery of ontogenetic decoding. The second major step will be solving the puzzle of differentiation.

A human being consists of 1 trillion cells of some two hundred different kinds, all derived by sequential division from the fertilized egg, a single cell 0.1 millimeter in diameter. The first few cell divisions yield a spherical mass of amorphous cells. Successive divisions are accompanied by the appearance of folds and ridges in the mass of cells and, later on, of the variety of tissues, organs, and limbs characteristic of a human individual. The full complement of genes duplicates with each cell division, so that two complete genomes are present in every cell. Moreover, experiments with other animals (and some with humans) indicate that all the genes in any cell have the potential of becoming activated.[5] Yet different sets of genes are active in different cells. This must be so in order for cells to differentiate: a nerve cell, a muscle cell, and a skin cell are vastly different in size, configuration, and function. The differential

activity of genes must continue after differentiation, because different cells fulfill different functions, which are controlled by different genes.

The information that controls cell and organ differentiation is, of course, ultimately contained in the DNA sequence, but probably only in very short segments of it. What sort of sequences are these controlling elements, where are they located, and how are they decoded? In mammals, insects, and other complex organisms, there are control circuits that operate at higher levels than the control mechanisms that activate and deactivate individual genes. These higher-level circuits (such as the so-called *homeobox* genes) act on sets rather than individual genes. The details of how these sets are controlled, how many control systems there are, and how they interact, as well as many other related questions, are what need to be resolved to elucidate the egg-to-adult transformation. The DNA sequence of some controlling elements has been ascertained, but this is a minor effort that is only helped a little by plowing the way through the entire three thousand million nucleotide pairs that constitute the human genome. Experiments with stem cells are likely to provide important knowledge as scientists ascertain how they become brain cells in one case, muscle cells in another, and so on.

The benefits that the elucidation of ontogenetic decoding will give to humankind are enormous. This knowledge will make possible the understanding of the modes of action of complex genetic diseases, including cancer, and therefore their cure. It will also confer an understanding of the process of aging, the unforgiving disease that kills all those who have won the battle against other infirmities.

Cancer is an anomaly of ontogenetic decoding: cells proliferate although the welfare of the organism demands otherwise. Individual genes (oncogenes) have been identified that are involved in the causation of particular forms of cancer. But whether or not a cell will turn out cancerous depends on the interaction of the oncogenes with other genes and with the internal and external environment of the cell. Aging is also a failure of the process of ontogenetic decoding: cells fail to carry out the functions imprinted in their genetic codescript or are no longer able to proliferate and replace dead cells.

In 1985, health care expenditures in the United States totaled $425 billion; in 2004 they surpassed $1 trillion. Most of these

expenditures go for supportive therapy and technological fixes that seek to compensate for the debilitating effects of diseases that we do not know how to prevent or truly cure. By contrast, those diseases whose causation is understood – tuberculosis, syphilis, smallpox, and viral childhood diseases, for example – can now be treated with relatively little cost and the best of results.[6] A mere 3 percent of the nation's total health care expenditures is devoted to basic research. Doubling or tripling this percentage would result in only a modest rise in total expenditures, but would yield large savings in the near future, as cancer, degenerative diseases, and other debilitating infirmities become preventable or curable, and thus no longer require the expensive and ultimately ineffectual therapy now in practice.

THE BRAIN-MIND PUZZLE

The brain is the most complex and most distinctive human organ. It consists of 30 billion nerve cells, or neurons, each connected to many others through two kinds of cell extensions, known as the axon and the dendrites. From the evolutionary point of view, the animal brain is a powerful biological adaptation; it allows the organism to obtain and process information about environmental conditions and then to adapt to them. This ability has been carried to the limit in humans, in which the extravagant hypertrophy of the brain makes possible abstract thinking, language, and technology. By these means, humankind has ushered in a new mode of adaptation far more powerful than the biological mode: adaptation by culture.

The most rudimentary ability to gather and process information about the environment is found in certain single-celled microorganisms. The protozoan *Paramecium* swims apparently at random, ingesting the bacteria it encounters, but when it meets unsuitable acidity or salinity, it checks its advance and starts in a new direction. The single-celled alga *Euglena* not only avoids unsuitable environments but seeks suitable ones by orienting itself according to the direction of light, which it perceives through a light-sensitive spot in the cell. Plants have not progressed much further. Except for those with tendrils that twist around any solid object and the few carnivorous plants that react to touch, they mostly react only to gradients of light, gravity, and moisture.

In animals the ability to secure and process environmental information is mediated by the nervous system. The simplest nervous systems are found in corals and jellyfishes; they lack coordination between different parts of their bodies, so any one part is able to react only when it is directly stimulated. Sea urchins and starfish possess a nerve ring and radial nerve cords that coordinate stimuli from different parts; hence, they respond with direct and unified actions of the whole body. They have no brain, however, and seem unable to learn from experience. Planarian flatworms have about the most rudimentary brain known; their central nervous system and brain process and coordinate information gathered by the sensory cells. These animals are capable of simple learning and hence of variable responses to repeatedly encountered stimuli. Insects and their relatives have much more advanced brains; they obtain precise chemical, acoustic, visual, and tactile signals from the environment and process them, making possible complex behaviors, particularly in their search for food and their selection of mates.

Vertebrates – animals with backbones – are able to obtain and process much more complicated signals and to respond to the environment more variably than insects or any other invertebrates. The vertebrate brain contains an enormous number of associative neurons arranged in complex patterns. In vertebrates the ability to react to environmental information is correlated with an increase in the relative size of the cerebral hemispheres and of the neopallium, an organ involved in associating and coordinating signals from all receptors and brain centers. In mammals, the neopallium has expanded and become the cerebral cortex. Humans have a very large brain relative to their body size, and a cerebral cortex that is disproportionately large and complex even for their brain size. Abstract thinking, symbolic language, complex social organization, values, and ethics are manifestations of the wondrous capacity of the human brain to gather information about the external world and to integrate that information and react flexibly to what is perceived.

With the advanced development of the human brain, biological evolution has transcended itself, opening up a new mode of evolution: adaptation by technological manipulation of the environment. Organisms adapt to the environment by means of natural selection, by changing their genetic constitution over the generations to suit the demands of the environment. Humans, and humans alone, have

developed the capacity to adapt to hostile environments by modifying the environments according to the needs of their genes. The discovery of fire and the fabrication of clothing and shelter have allowed humans to spread from the warm tropical and subtropical regions of the Old World, to which we are biologically adapted, to almost the whole Earth; it was not necessary for the wandering humans that they wait until genes would evolve providing anatomical protection by means of fur or hair. Nor are humans biding their time in expectation of wings or gills; we have conquered the air and seas with artfully designed contrivances, airplanes and ships. It is the human brain (the human mind) that has made humankind the most successful living species, by most meaningful standards.

There are not enough bits of information in the complete DNA sequence of a human genome to specify the trillions of connections among the 30 billion neurons of the human brain. Accordingly, the genetic instructions must be organized in control circuits operating at different hierarchical levels, as described earlier, so that an instruction at one level is carried through many channels at a lower level in the hierarchy of control circuits. The development of the human brain is indeed one particularly intriguing component of the egg-to-adult transformation. But we must focus now on the issue at hand, namely, how this awesome organ, the human brain, works.

Within the last two decades, neurobiology has developed into one of the most exciting biological disciplines. An increased commitment of financial and human resources has yielded an unprecedented rate of discovery. Much has been learned about how light, sound, temperature, resistance, and chemical impressions received in our sense organs trigger the release of chemical transmitters and electric potential differences that carry the signals through the nerves to the brain and elsewhere in the body. Much has also been learned about how neural channels for information transmission become reinforced by use or may be replaced after damage, about which neurons or groups of neurons are committed to processing information derived from a particular organ or environmental location, and about many other matters. But, for all this progress, neurobiology remains an infant discipline, at a stage of theoretical development comparable perhaps to that of genetics at the beginning of the twentieth century. Those things that count most remain shrouded in mystery: how physical phenomena become mental

experiences (the feelings and sensations, called ''qualia'' by philosophers, that contribute the elements of consciousness), and how out of the diversity of these experiences emerges the mind, a reality with unitary properties, such as free will and the awareness of self, that persist through an individual's life.

I do not believe that these mysteries are unfathomable; rather, they are puzzles that the human mind can solve with the methods of science and illuminate with philosophical analysis and reflection. And I will place my bets that, over the next half-century or so, many of these puzzles will be solved. We shall then be well on our way toward answering the injunction ''Know thyself.''

THE APE-TO-HUMAN TRANSFORMATION

Knowing the human DNA sequence is a first step, but no more than one step, towards understanding the genetic makeup of a human being. Think of the one thousand Bible-sized volumes. We now know the orderly sequence of the three thousand million letters, but this sequence does not provide an understanding of human beings any more than we would understand the contents of one thousand Bible-sized volumes written in an extraterrestrial language, of which we only know the alphabet, just because we would have deciphered their letter sequence.

Human beings are not gene machines. The expression of genes in mammals takes place in interaction with the environment, in patterns that are complex and all but impossible to predict in the details – and it is in the details that the self resides. In humans, the ''environment'' takes a new dimension, which becomes the dominant one. Humans manipulate the natural environment so that it fits the needs of their biological makeup, for example, using clothing and housing to live in cold climates. Moreover, the products of human technology, art, science, political institutions, and the like, become a dominant feature of the human environment. As I have mentioned earlier, a distinctive characteristic of human evolution is adaptation by means of ''culture,'' which may be understood as the set of non–strictly biological human activities and creations.

Two conspicuous features of human anatomy 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 minor exception); kangaroos are mostly bipedal, but without proper erect posture or bipedal gait. Brain size is generally proportional to body size; relative to body mass, humans have the largest (and most complex) brain. The chimpanzee's brain weighs less than a pound; a gorilla's slightly more. The human male adult brain has a volume of 1,400 cubic centimeters (cc), about three pounds in weight.

In earlier decades, evolutionists raised the question whether bipedal gait or large brain occured first, or whether they evolved consonantly. The issue is now resolved. Our hominid ancestors had, since at least four million years ago, a bipedal gait, but their brain was still small, no more than 450 cc, a pound in weight, until about two million years ago. Brain size started to increase notably with our *Homo habilis* ancestors, who had a brain about 650 cc and also became tool-makers (hence the name *habilis*), and who lived for a few hundred thousand years, starting about two and a half million years ago. Their immediate descendants were *Homo erectus*, with adult brains reaching up to 1,200 cc in size. (I use the name *Homo erectus*, as it is often used, in a broad sense that encompasses a fairly diverse group of ancestors and their relatives, which current paleoanthropologists classify in several species, including *Homo ergaster*, *Homo antecessor*, and *Homo heidelbergensis*.) Our species, *Homo sapiens*, has a brain of 1,300–1,400 cc, about three times as large as that of the early hominids. Our brain is not only much larger than that of chimpanzees or gorillas, but also much more complex. The cerebral cortex, where the higher cognitive functions are processed, is in humans disproportionally much greater than the rest of the brain when compared to that of apes.

BIOLOGICAL EVOLUTION VERSUS CULTURAL EVOLUTION

Culture, as I define it here, has an individual and a social component. It includes ideas, habits, dispositions, preferences, values, and beliefs of each individual. It also includes the public results of human intellectual activity; technology; humanistic and scientific knowledge; literature, music, and art; codes of law and social and political institutions; ethical codes and religious systems. The individual and social components of culture correspond to the World

2 and World 3 of the eminent philosopher Karl Popper. The difference between the two becomes apparent when we consider that the extinction of humankind on Earth would eliminate World 2, while World 3 could survive in part or on the whole and could be assimilated by humans or humanoids from a different planet. The advent of culture 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.

There are in humankind two kinds of heredity – the biological and the cultural – which may also be called organic and superorganic, or endosomatic and exosomatic systems of heredity. Biological inheritance in humans is very much like that in any other sexually reproducing organism; it is based on the transmission of genetic information encoded in DNA from one generation to the next by means of the sex cells.

Cultural inheritance, in contrast, is based on transmission of information by a teaching-learning process, which is in principle independent of biological parentage. Culture is transmitted by instruction and learning, by example and imitation, through books, newspapers and radio, television and motion pictures, through works of art, and by any other means of communication. Culture is acquired by every person from parents, relatives, and neighbors and from the whole human environment (Dobzhansky 1962, Ehrlich 2000, Cavalli-Sforza and Feldman 1981, Boyd and Richerson 1985, Richerson and Boyd 2005).

Cultural inheritance makes possible for humans what no other organism can accomplish – the cumulative transmission of experience from generation to generation. Animals can learn from experience, but they do not transmit their experiences, their ''discoveries'' (at least not to any large extent) to the following generations. Animals have individual memory, but they do not have a ''social memory.'' Humans, on the other hand, have developed a culture because they can transmit cumulatively their experiences from generation to generation. Some cultural transmission has been identified in chimpanzees and orangutan populations, but the ''cultures'' developed by these apes amount to trivial rudiments when compared to human cultures (Whiten et al. 1999, Whiten 2005).

Cultural inheritance makes possible cultural evolution, a new mode of adaptation to the environment that is not available to

nonhuman organisms – adaptation by means of culture. Organisms in general adapt to the environment by means of natural selection, by changing over generations their genetic constitution to suit the demands of the environment. But humans, and humans alone, can also adapt by changing the environment to suit the needs of their genes. (Some animals build nests and modify their environment also in other ways, but the manipulation of the environment by any nonhuman species is trivial compared to humankind's, even in the case of the apes.)

For the last few millennia, humans have been adapting the environments to their genes more often than their genes to the environments. In order to extend its geographical habitat, or to survive in a changing environment, a population of organisms must become adapted, through slow accumulation of genetic variants sorted out by natural selection, to the new climatic conditions, different sources of food, different competitors, and so on. The discovery of fire and the use of shelter and clothing allowed humans to spread from the warm tropical and subtropical regions of the Old World to the whole Earth, except for the frozen wastes of Antarctica, without the anatomical development of fur or hair. Humans did not wait for genetic mutants promoting wing development; they have conquered the air in a somewhat more efficient and versatile way by building flying machines. People travel the rivers and the seas without gills or fins. The exploration of outer space has started without waiting for mutations providing humans with the ability to breathe under low oxygen pressures or to function in the absence of gravity; astronauts carry their own oxygen and specially equipped pressure suits. From their obscure beginnings in Africa, humans have become the most widespread and abundant species of mammal on Earth. It was the appearance of culture as a superorganic form of adaptation that made humankind the most successful animal species.

Whenever a need arises, humans can directly pursue the appropriate cultural "mutations," that is, design changes to meet the challenge. These changes are the discoveries and inventions that pervade human life. The invention and use of fire, the construction of bridges and skyscrapers, the telephone and the Internet, are examples of technological cultural mutations; science, art, political institutions, codes of ethics and religious systems also are cultural

mutations. On the contrary, biological adaptation depends on the accidental availability of a favorable mutation, or of a combination of several mutations, at the time and place where the need arises.

Cultural heredity and biological heredity drastically differ in their mode of transmission, with important consequences in the speed with which a favorable adaptation spreads. Biological heredity is transmitted only vertically, from parents to their offspring, while cultural heredity spreads "horizontally" as well as vertically, as noted earlier. A favorable genetic mutation newly arisen in an individual can be transmitted to a sizable part of the human species only through innumerable generations. However, a new scientific discovery or technical innovation can be transmitted to the whole of humankind, potentially at least, in less than one generation. Witness the worldwide spread of cellular phones or the Internet in less than a decade or of the personal computer in less than a quarter-century.

Biological heredity is Mendelian because only the genes received from one's own parents are transmitted to the progeny. (The presence in an individual of newly acquired gene variations by spontaneous mutation does not materially challenge this statement.) But acquired characteristics, that is, the inventions, technological developments, and any kind of learning or experience acquired throughout an individual's life, can all be transmitted to other humans, whether or not they are direct descendants of the individual. Cultural heredity is Lamarckian in this sense, because "acquired characteristics," and not only inherited ones, can be transmitted to others.

The draft DNA sequence of the chimpanzee genome was published on 1 September 2005.[7] In the genome regions shared by humans and chimpanzees, the two species are 99 percent identical. The differences appear to be very small or quite large, depending on how one chooses to look at them: 1 percent of the total seems very little, but it amounts to a difference of 30 million DNA letters out of the three billion in each genome. Of the enzymes and other proteins encoded by the genes, 29 percent are identical in both species. Out of the one hundred to several hundred amino acids that make up each protein, the 71 percent of nonidentical proteins differ by only two amino acids, on the average. The two genomes are about 96 percent identical if one takes into account DNA stretches found in one species but not the other. That is, a large amount of genetic material,

about 3 percent or some 90 million DNA letters, has been inserted or deleted since humans and chimps initiated their separate evolutionary ways, 7 or 8 million years ago. Most of this DNA does not seem to contain genes coding for proteins.

Comparison of the two genomes provides insights into the rate of evolution of particular genes in the two species. One significant finding is that genes active in the brain have changed more in the human lineage than in the chimp lineage. Also significant is that the fastest evolving human genes are those coding for ''transcription factors.'' These are ''switch'' proteins, which control the expression of other genes, that is, when they are turned on and off. On the whole, 585 genes have been identified as evolving faster in humans, including genes involved in resistance to malaria and tuberculosis. (It might be mentioned that malaria is a much more severe disease for humans than for chimps.) Genes located in the Y chromosome (the chromosome that determines maleness; females have two X chromosomes; males have one X and Y chromosome, the Y being much smaller than the X) have been much better protected by natural selection in the human than in the chimpanzee lineage, where several genes have incorporated disabling mutations that make the genes nonfunctional. There are several regions of the human genome that seem to contain beneficial genes that have rapidly evolved within the past 250,000 years. One region contains the *FOXP2* gene, which had earlier been discovered to be involved in the evolution of speech.

Extended comparisons of the human and chimp genomes and experimental exploration of the functions associated with significant genes will surely advance considerably our understanding, over the next decade or two, of what it is that accounts for the *humanum*, what makes us distinctively human. Surely also, full understanding will only result from the joint solution of the three conundrums that I have identified. The distinctive features that make us human begin early in development, well before birth, as the linear information encoded in the genome gradually becomes expressed into a four-dimensional individual. In an important sense, the most distinctive human features are those expressed in the brain, those that account for the human mind and for human identity. It is human intelligence that makes possible human culture.

NOTES

1. Cited by D. Nelkin and M. S. Lindee, *The DNA Mystique. The Gene as a Cultural Icon*, W. H. Freeman, New York, 1995, p. 7.
2. Quoted in Leon Jaroff, ''The Gene Hunt,'' *Time*, 20 March 1989, pp. 62–67.
3. D. Roshland, ''Elephants, Monstrosities and the Law,'' *Science* 25 (4 February 1992), p. 777.
4. I am not challenging here that the Human Genome Project has many public health applications or that the deciphering of the genomes of other species is of great consequence in health care, agriculture, animal husbandry, and industry. The question is how much it can contribute to solve the three fundamental problems faced by human biology that I am expounding.
5. The sheep ''Dolly'' was conceived using genes extracted from a cell in an adult sheep.
6. This statement is overly optimistic, and it may be outright erroneous if the phrase ''understood causation'' is not precisely construed. Malaria and AIDS are two diseases whose causation is understood at a number of levels, yet we fail to treat them ''with relatively little cost and the best results.'' In any case, one can anticipate that increased knowledge of the etiology of these diseases may lead to successful development of effective vaccines or drugs.
7. *Nature* 437 (1 September 2005); see also *Science* 309 (2 September 2005).