CrossMark click for updates

Cloning humans? Biological, ethical, and social considerations

Francisco J. Ayala[1]

Department of Ecology and Evolutionary Biology, University of California, Irvine, CA 92697

Edited by John C. Avise, University of California, Irvine, CA, and approved March 11, 2015 (received for review February 27, 2015)

There are, in mankind, two kinds of heredity: biological and cultural. Cultural inheritance makes possible for humans what no other organism can accomplish: the cumulative transmission of experience from generation to generation. In turn, cultural inheritance leads to cultural evolution, the prevailing mode of human adaptation. For the last few millennia, humans have been adapting the environments to their genes more often than their genes to the environments. Nevertheless, natural selection persists in modern humans, both as differential mortality and as differential fertility, although its intensity may decrease in the future. More than 2,000 human diseases and abnormalities have a genetic causation. Health care and the increasing feasibility of genetic therapy will, although slowly, augment the future incidence of hereditary ailments. Germline gene therapy could halt this increase, but at present, it is not technically feasible. The proposal to enhance the human genetic endowment by genetic cloning of eminent individuals is not warranted. Genomes can be cloned; individuals cannot. In the future, therapeutic cloning will bring enhanced possibilities for organ transplantation, nerve cells and tissue healing, and other health benefits.

human origins | natural selection | cultural evolution | genetic therapy | therapeutic cloning

Chimpanzees are the closest relatives of *Homo sapiens*, our species. There is a precise correspondence bone by bone between the skeletons of a chimpanzee and a human. Humans bear young like apes and other mammals. Humans have organs and limbs similar to birds, reptiles, and amphibians; these similarities reflect the common evolutionary origin of vertebrates. However, it does not take much reflection to notice the distinct uniqueness of our species. Conspicuous anatomical differences between humans and apes include bipedal gait and an enlarged brain. Much more conspicuous than the anatomical differences are the distinct behaviors and institutions. Humans have symbolic language, elaborate social and political institutions, codes of law, literature and art, ethics, and religion; humans build roads and cities, travel by motorcars, ships, and airplanes, and communicate by means of telephones, computers, and televisions.

Human Origins

The hominin lineage diverged from the chimpanzee lineage 6–7 Ma, and it evolved exclusively in the African continent until the emergence of *Homo erectus*, somewhat before 1.8 Ma. Shortly after its emergence in tropical or subtropical Africa, *H. erectus* spread to other continents. Fossil remains of *H. erectus* (sensu lato) are known from Africa, Indonesia (Java), China, the Middle East, and Europe. *H. erectus* fossils from Java have been dated at 1.81 ± 0.04 and 1.66 ± 0.04 Ma and from Georgia at 1.6–1.8 Ma (1). Anatomically distinctive *H. erectus* fossils have been found in Spain, deposited before 780,000 y ago, the oldest in southern Europe (2).

The transition from *H. erectus* to *H. sapiens* occurred around 400,000 y ago, although this date is not well determined owing to uncertainty as to whether some fossils are *erectus* or archaic forms of *sapiens*. *H. erectus* persisted for some time in Asia, until 250,000 y ago in China and perhaps until 100,000 ago in Java, and thus was contemporary with early members of its descendant species, *H. sapiens*. Fossil remains of Neandertal hominids (*Homo neanderthalensis*), with brains as large as those of *H. sapiens*, appeared in Europe earlier than 200,000 y ago and persisted until 30,000 or 40,000 y ago (3, 4).

There is controversy about the origin of modern humans. 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" emphasize fossil evidence showing regional continuity in the transition from *H. erectus* to archaic and then modern *H. sapiens*. Most anthropologists argue instead that modern humans first arose in Africa somewhat before 100,000 y ago and from there spread throughout the world, eventually replacing elsewhere the preexisting populations of *H. erectus*, *H. neanderthalensis,* and archaic *H. sapiens*. The African origin of modern humans is supported by a wealth of recent genetic evidence and is therefore favored by many evolutionists (2, 4).

We know about these matters in three ways: by comparing living primates, including humans, with each other; by discovery and investigation of fossil remains of primates that lived in the past; and by comparing their DNA, proteins, and other molecules. DNA and proteins give us the best information about how closely related we are to each of the primates and those to each other. However, to know how the human lineage changed in anatomy and behavior over time as our ancestors became more and more human-like, we have to study fossils and the tools they used and made, as well as other remnants of their activities (2, 5).

Humans live in groups that are socially organized and so do other primates. However, other primate societies do not approach the complexity of human social organization. A distinctive human social trait is culture, which may be understood as the set of nonstrictly biological human activities and creations. Culture 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. The advent of culture has brought with it cultural evolution, a superorganic mode of evolution superimposed on the organic mode, that has become the dominant mode of human evolution. Cultural evolution has come about because of cultural inheritance, a distinctively human mode of achieving adaptation to the environment (2, 6, 7).

There are in mankind two kinds of heredity: the biological and the cultural. 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

This paper results from the Arthur M. Sackler Colloquium of the National Academy of Sciences, "In the Light of Evolution IX: Clonal Reproduction: Alternatives to Sex," held January 9–10, 2015, at the Arnold and Mabel Beckman Center of the National Academies of Sciences and Engineering in Irvine, CA. The complete program and video recordings of most presentations are available on the NAS website at www.nasonline.org/ILE_IX_Clonal_Reproduction.

Author contributions: F.J.A. wrote the paper.

The author declares no conflict of interest.

This article is a PNAS Direct Submission.

[1]Email: fjayala@uci.edu.

inheritance, on the other hand, 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, radio, television, and motion pictures, through works of art, and through any other means of communication. Culture is acquired by every person from parents, relatives, and neighbors and from the whole human environment. Acquired cultural traits may be beneficial but also toxic; for example, racial prejudice or religious bigotry.

Biological heredity is Mendelian or vertical; it is transmitted from parents to their children, and only inherited traits can be transmitted to the progeny. (New mutations are insignificant in the present context.) Cultural heredity is Lamarckian: acquired characters can be transmitted to the progeny. However, cultural heredity goes beyond Lamarckian heredity, because it is horizontal and oblique and not only vertical. Traits can be acquired from and transmitted to other members of the same generation, whether or not they are relatives, and also from and to all other individuals with whom a person has contact, whether they are from the same or from any previous or ensuing generation.

Cultural inheritance makes possible for people 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 or 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.

Cultural inheritance makes possible cultural evolution, a new mode of adaptation to the environment that is not available to nonhuman organisms. 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. However, humans, and humans alone, can also adapt by changing the environment to suit the needs of their genes. (Animals build nests and modify their environment also in other ways, but the manipulation of the environment by any nonhuman species is trivial compared with mankind's manipulation.) For the last few millennia, humans have been adapting the environments to their genes more often than their genes to the environments.

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 with 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 mankind the most successful animal species.

Cultural adaptation has prevailed in mankind over biological adaptation because it is a more effective mode of adaptation; it is more rapid and it can be directed. A favorable genetic mutation newly arisen in an individual can be transmitted to a sizeable part of the human species only through innumerable generations. However, a new scientific discovery or technical achievement can be transmitted to the whole of mankind, potentially at least, in less than one generation. Witness the rapid spread of personal computers, iPhones, and the Internet. Moreover, whenever a need arises, culture can directly pursue the appropriate changes to meet the challenge. 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 (2, 6, 7).

Biological Evolution in Modern Humans

There is no scientific basis to the claim sometimes made that the biological evolution of mankind has stopped, or nearly so, at least in technologically advanced countries. It is asserted that the progress of medicine, hygiene, and nutrition have largely eliminated death before middle age; that is, most people live beyond reproductive age, after which death is inconsequential for natural selection. That mankind continues to evolve biologically can be shown because the necessary and sufficient conditions for biological evolution persist. These conditions are genetic variability and differential reproduction. There is a wealth of genetic variation in mankind. With the trivial exception of identical twins, developed from a single fertilized egg, no two people who live now, lived in the past, or will live in the future, are likely to be genetically identical. Much of this variation is relevant to natural selection (5, 8, 9).

Natural selection is simply differential reproduction of alternative genetic variants. Natural selection will occur in mankind if the carriers of some genotypes are likely to leave more descendants than the carriers of other genotypes. Natural selection consists of two main components: differential mortality and differential fertility; both persist in modern mankind, although the intensity of selection due to postnatal mortality has been somewhat attenuated.

Death may occur between conception and birth (prenatal) or after birth (postnatal). The proportion of prenatal deaths is not well known. Death during the early weeks of embryonic development may go totally undetected. However, it is known that no less than 20% of all ascertained human conceptions end in spontaneous abortion during the first 2 mo of pregnancy. Such deaths are often due to deleterious genetic constitutions, and thus they have a selective effect in the population. The intensity of this form of selection has not changed substantially in modern mankind, although it has been slightly reduced with respect to a few genes such as those involved in Rh blood group incompatibility.

Postnatal mortality has been considerably reduced in recent times in technologically advanced countries. For example, in the United States, somewhat less than 50% of those born in 1840 survived to age 45, whereas the average life expectancy for people born in the United States in 1960 is 78 y (Table 1) (8, 10). In some regions of the world, postnatal mortality remains quite high, although there it has also generally decreased in recent decades. Mortality before the end of reproductive age, particularly where it has been considerably reduced, is largely associated with genetic defects, and thus it has a favorable selective effect in human populations. Several thousand genetic variants are known that cause diseases and malformations in humans; such variants are kept at low frequencies due to natural selection.

It might seem at first that selection due to differential fertility has been considerably reduced in industrial countries as a consequence of the reduction in the average number of children per family that has taken place. However, this is not so. The intensity of fertility selection depends not on the mean number of children per family, but on the variance in the number of children per family. It is clear why this should be so. Assume that all people of reproductive age marry and that all have exactly the same number of children. In this case, there would not be fertility selection whether couples all had very few or all had very many

Table 1. Percent of Americans born between 1840 and 1960 surviving to ages 15 and 45

	Surviving to age 15 (%)		Surviving to age 45 (%)	
Birth	Men	Women	Men	Women
1840	62.8	66.4	48.2	49.4
1880	71.5	73.1	58.3	61.1
1920	87.6	89.9	79.8	85.8
1960	99.0	99.2	94.1	96.1

Reprinted from ref. 8.

children. Assume, on the other hand, that the mean number of children per family is low, but some families have no children at all or very few, whereas others have many. In this case, there would be considerable opportunity for selection—the genotypes of parents producing many children would increase in frequency at the expense of those having few or none. Studies of human populations have shown that the opportunity for natural selection often increases as the mean number of children decreases. An extensive study published years ago showed that the index of opportunity for selection due to fertility was four times larger among United States women born in the 20th century, with an average of less than three children per woman, than among women in the Gold Coast of Africa or in rural Quebec, who had three times or more children on average (Table 2) (8, 11). There is no evidence that natural selection due to fertility has decreased in modern human populations.

Natural selection may decrease in intensity in the future, but it will not disappear altogether. As long as there is genetic variation and the carriers of some genotypes are more likely to reproduce than others, natural selection will continue operating in human populations. Cultural changes, such as the development of agriculture, migration from the country to the cities, environmental pollution, and many others, create new selective pressures. The pressures of city life are partly responsible for the high incidence of mental disorders in certain human societies. The point to bear in mind is that human environments are changing faster than ever owing precisely to the accelerating rate of cultural change, and environmental changes create new selective pressures, thus fueling biological evolution.

Natural selection is the process of differential reproduction of alternative genetic variants. In terms of single genes, variation occurs when two or more alleles are present in the population at a given gene locus. How much genetic variation exists in the current human population? The answer is "quite a lot," as will be presently shown, but natural selection will take place only if the alleles of a particular gene have different effects on fitness; that is, if alternative alleles differentially impact the probability of survival and reproduction.

The two genomes that we inherit from each parent are estimated to differ at about one or two nucleotides per thousand. The human genome consists of somewhat more than 3 billion nucleotides (12). Thus, about 3–6 million nucleotides are different between the two genomes of each human individual, which is a lot of genetic polymorphism. Moreover, the process of mutation introduces new variation in any population every generation. The rate of mutation in the human genome is estimated to be about 10^{-8}, which is one nucleotide mutation for every hundred million nucleotides, or about 30 new mutations per genome per generation. Thus, every human has about 60 new mutations (30 in each genome) that were not present in the parents. If we consider the total human population, that is 60 mutations per person multiplied by 7 billion people, which is about 420 billion new mutations per generation that are added to the preexisting 3–6 million polymorphic nucleotides per individual.

That is a lot of mutations, even if many are redundant. Moreover, we must remember that the polymorphisms that count for natural selection are those that impact the probability of survival and reproduction of their carriers. Otherwise, the variant nucleotides may increase or decrease in frequency by chance, a process that evolutionists call "genetic drift," but will not be impacted by natural selection (2, 12, 13).

Genetic Disorders

More than 2,000 human diseases and abnormalities that have a genetic causation have been identified in the human population. Genetic disorders may be dominant, recessive, multifactorial, or chromosomal. Dominant disorders are caused by the presence of a single copy of the defective allele, so that the disorder is expressed in heterozygous individuals: those having one normal and one defective allele. In recessive disorders, the defective allele must be present in both alleles, that is, it is inherited from each parent to be expressed. Multifactorial disorders are caused by interaction among several gene loci; chromosomal disorders are due to the presence or absence of a full chromosome or a fragment of a chromosome (14, 15).

Examples of dominant disorders are some forms of retinoblastoma and other kinds of blindness, achondroplastic dwarfism, and Marfan syndrome (which is thought to have affected President Lincoln). Examples of recessive disorders are cystic fibrosis, Tay-Sachs disease, and sickle cell anemia (caused by an allele that in heterozygous condition protects against malaria). Examples of multifactorial diseases are spina bifida and cleft palate. Among the most common chromosomal disorders are Down syndrome, caused by the presence of an extra chromosome 21, and various kinds due to the absence of one sex chromosome or the presence of an extra one, beyond the normal condition of XX for women and XY for men. Examples are Turner's syndrome (XO) and Klinefelter's syndrome (XXY) (16).

Table 2. Mean number of children per family and index of opportunity for fertility selection I_f, in various human populations

Population	Mean number of children	I_j
Rural Quebec, Canada	9.9	0.20
Gold Coast, Africa	6.5	0.23
New South Wales, Australia (1898–1902)	6.2	0.42
United States, women born in 1839	5.5	0.23
United States, women born in 1871–1875	3.5	0.71
United States, women born in 1928	2.8	0.45
United States, women born in 1909	2.1	0.88
United States, Navajo Indians	2.1	1.57

I_f is calculated as the variance divided by the square of the mean number of children. The opportunity for selection usually increases as the mean number of children decreases. Reprinted from ref. 8.

The incidence of genetic disorders expressed in the living human population is estimated to be no less than 2.56%, impacting about 180 million people. Natural selection reduces the incidence of the genes causing disease, more effectively in the case of dominant disorders, where all carriers of the gene will express the disease, than for recessive disorders, which are expressed only in homozygous individuals. Consider, for example, phenylketonuria (PKU), a lethal disease if untreated, due to homozygosis for a recessive gene, which has an incidence of 1 in 10,000 newborns or 0.01%. PKU is due to an inability to metabolize the amino acid phenylalanine with devastating mental and physical effects. A very elaborate diet free of phenylalanine allows the patient to survive and reproduce if started early in life. The frequency of the PKU allele is about 1%, so that in heterozygous conditions it is present in more than 100 million people, but only the 0.01% of people who are homozygous express the disease and are subject to natural selection. The reduction of genetic disorders due to natural selection is balanced with their increase due to the incidence of new mutations.

Let's consider another example. Hereditary retinoblastoma is a disease attributed to a dominant mutation of the gene coding for the retinoblastoma protein, RB1, but it is actually due to a deletion in chromosome 13. The unfortunate child with this condition develops a tumorous growth during infancy that, without treatment, starts in one eye and often extends to the other eye and then to the brain, causing death before puberty. Surgical treatment now makes it possible to save the life of the child if the condition is detected sufficiently early, although often one or both eyes may be lost. The treated person can live a more or less normal life, marry, and procreate. However, because the genetic determination is dominant (a gene deletion), one half of the progeny will, on the average, be born with the same genetic condition and will have to be treated. Before modern medicine, every mutation for retinoblastoma arising in the human population was eliminated from the population in the same generation owing to the death of its carrier. With surgical treatment, the mutant condition can be preserved, and new mutations arising each generation are added to those arisen in the past (refs. 17 and 18; www.abedia.com/wiley/index.html).

The proportion of individuals affected by any one serious hereditary infirmity is relatively small, but there are more than 2,000 known serious physical infirmities determined by genes. When all these hereditary ailments are considered together, the proportion of persons born who will suffer from a serious handicap during their lifetimes owing to their heredity is more than 2% of the total population, as pointed out above (refs. 15, 16, and 19; www.abedia.com/wiley/index.html).

The problem becomes more serious when mental defects are taken into consideration. More than 2% of the population is affected by schizophrenia or a related condition known as schizoid disease, ailments that may be in some cases determined by a single mutant gene. Another 3% or so of the population suffer from mild mental retardation (IQ less than 70). More than 100 million people in the world suffer from mental impairments due in good part to the genetic endowment they inherited from their parents.

Natural selection also acts on a multitude of genes that do not cause disease. Genes impact skin pigmentation, hair color and configuration, height, muscle strength and body shape, and many other anatomical polymorphisms that are apparent, as well as many that are not externally obvious, such as variations in the blood groups, in the immune system, and in the heart, liver, kidney, pancreas, and other organs. It is not always known how natural selection impacts these traits, but surely it does and does it differently in different parts of the world or at different times, as a consequence of the development of new vaccines, drugs, and medical treatments, and also as a consequence of changes in lifestyle, such as the reduction of the number of smokers or the increase in the rate of obesity in a particular country.

Genetic Therapy

Where is human evolution going? Biological evolution is directed by natural selection, which is not a benevolent force guiding evolution toward sure success. Natural selection brings about genetic changes that often appear purposeful because they are dictated by the requirements of the environment. The end result may, nevertheless, be extinction—more than 99.9% of all species that ever existed have become extinct. Natural selection has no purpose; humans alone have purposes and they alone may introduce them into their evolution. No species before mankind could select its evolutionary destiny; mankind possesses techniques to do so, and more powerful techniques for directed genetic change are becoming available. Because we are self-aware, we cannot refrain from asking what lies ahead, and because we are ethical beings, we must choose between alternative courses of action, some of which may appear as good and others as bad.

The argument has been advanced that the biological endowment of mankind is rapidly deteriorating owing precisely to the improving conditions of life and to the increasing power of modern medicine. The detailed arguments that support this contention involve some mathematical exercises, but their essence can be simply presented. Genetic changes (i.e., point or chromosome mutations) arise spontaneously in humans and in other living species. The great majority of newly arising mutations are either neutral or harmful to their carriers; only a very small fraction are likely to be beneficial. In a human population under the so-called "natural" conditions, that is, without the intervention of modern medicine and technology, the newly arising harmful mutations are eliminated from the population more or less rapidly depending on how harmful they are. The more harmful the effect of a mutation, the more rapidly it will be eliminated from the population by the process of natural selection. However, owing to medical intervention and, more recently, because of the possibility of genetic therapy, the elimination of some harmful mutations from the population is no longer taking place as rapidly and effectively as it did in the past.

Molecular biology has introduced in modern medicine a new way to cure diseases, namely genetic therapy, direct intervention in the genetic makeup of an individual. Gene therapy can be somatic or germ line. Germ-line genetic therapy would seek to correct a genetic defect, not only in the organs or tissues impacted, but also in the germ line, so that the person treated would not transmit the genetic impairment to the descendants. As of now, no interventions of germ-line therapy are seriously sought by scientists, physicians, or pharmaceutical companies.

The possibility of gene therapy was first anticipated in 1972 (20). The possible objectives are to correct the DNA of a defective gene or to insert a new gene that would allow the proper function of the gene or DNA to take place. In the case of a harmful gene, the objective would be to disrupt the gene that is not functioning properly.

The eminent biologist E. O. Wilson (2014) has stated, many would think somewhat hyperbolically, that the issue of how much to use genetic engineering to direct our own evolution, is "the greatest moral dilemma since God stayed the hand of Abraham" (21).

The first successful interventions of gene therapy concerned patients suffering from severe combined immunodeficiency (SCID), first performed in a 4-y-old girl at the National Institutes of Health in 1990 (22), soon followed by successful trials in other countries (23). Treatments were halted temporarily from 2000 to 2002 in Paris, when 2 of about 12 treated children developed a leukemia-like condition, which was indeed attributed to the gene therapy treatment. Since 2004, successful clinical trials for SCID have been performed in the United States, United Kingdom, France, Italy, and Germany (24, 25).

Gene therapy treatments are still considered experimental. Successful clinical trials have been performed in patients suffering from adrenoleukodystrophy, Parkinson's disease, chronic

lymphocytic leukemia, acute lymphocytic leukemia, multiple myeloma, and hemophilia (26, 27). Initially, the prevailing gene therapy methods involved recombinant viruses, but nonviral methods (transfection molecules) have become increasingly successful. Since 2013, US pharmaceutical companies have invested more than $600 million in gene therapy (28). However, in addition to the huge economic costs, technical hurdles remain. Frequent negative effects include immune response against an extraneous object introduced into human tissues, leukemia, tumors, and other disorders provoked by vector viruses. Moreover, the genetic therapy corrections are often short lived, which calls for multiple rounds of treatment, thereby increasing costs and other handicaps. In addition, many of the most common genetic disorders are multifactorial and are thus beyond current gene therapy treatment. Examples are diabetes, high blood pressure, heart disease, arthritis, and Alzheimer's disease, which at the present state of knowledge and technology are not suitable for gene therapy.

If a genetic defect is corrected in the affected cells, tissues, or organs, but not in the germ line, the ova or sperm produced by the individual will transmit the defect to the progeny. A deleterious gene that might have been reduced in frequency or eliminated from the population, owing to the death or reduced fertility of the carrier, will now persist in the population and be added to its load of hereditary diseases. A consequence of genetic therapy is that the more hereditary diseases and defects are cured today, the more of them will be there to be cured in the succeeding generations. This consequence follows not only from gene therapy but also from typical medical treatments.

The Nobel laureate geneticist H. J. Muller eloquently voiced this concern about the cure, whether through genetic therapy or traditional medical treatment, of genetic ailments. "The more sick people we now cure and allow them to reproduce, the more there will be to cure in the future." The fate toward which mankind is drifting is painted by Muller in somber colors. "The amount of genetically caused impairment suffered by the average individual. . .must by that time have grown. . ..[P]eople's time and energy. . .would be devoted chiefly to the effort to live carefully, to spare and to prop up their own feebleness, to soothe their inner disharmonies and, in general, to doctor themselves as effectively as possible. For everyone would be an invalid, with his own special familial twists. . .." (ref. 29; Fig. 1).

It must be pointed out that the population genetic consequences of curing hereditary diseases are not as immediate ("a few centuries hence") as Muller anticipates. Consider, as a first example, we look at the recessive hereditary condition of PKU. The estimated frequency of the gene is $q = 0.01$; the expected number of humans born with PKU is $q^2 = 0.0001$, 1 for every 10,000 births. If all PKU individuals are cured all over the world and all of them leave as many descendants, on the average, as other humans, the frequency of the PKU allele will double after $1/q = 1/0.01 = 100$ generations. If we assume 25 y per generation, we conclude that after 2,500 y, the frequency of the PKU allele will be $q = 0.02$, and $q^2 = 0.0004$, so that 4 of every 10,000 persons, rather than only 1, will be born with PKU.

In the case of dominant lethal diseases, the incidence is determined by the mutation frequency of the normal to the disease allele, which is typically of the order of $m = 10^{-6}$–10^{-8}, or between one in a million and one in one hundred million. Assuming the highest rate of $m = 10^{-6}$, the incidence of the disease after 100 generations will become 1 for every 10,000 births. It would therefore seem likely that much earlier than 2,500 y, humans are likely to find ways of correcting hereditary ailments in the germ line, thereby stopping their transmission.

It must be pointed out that, although the proportion of individuals affected by any one serious hereditary infirmity is relatively small, there are many such hereditary ailments, which on the aggregate make the problem very serious. The problem becomes more serious when mental defects are taken into consideration. As pointed out above, more than 100 million people in the world suffer from mental impairments due in good part to the genetic endowment they inherited from their parents.

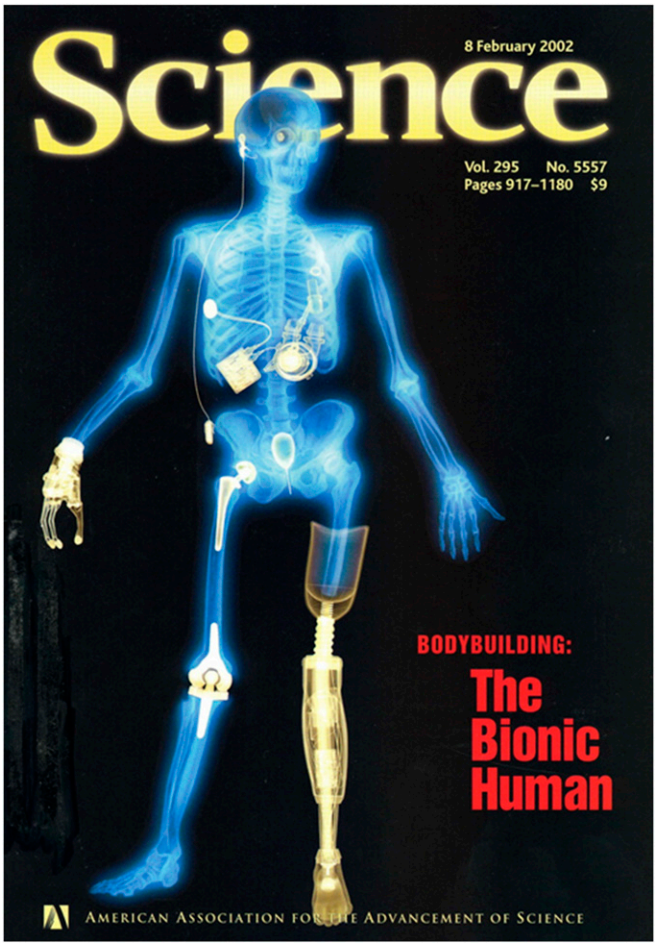

Fig. 1. The bionic human, on the cover of *Science*: an image that could represent how H. J. Muller anticipates the human condition, a few centuries hence, showing the accumulation of physical handicaps as a consequence of the medical cure of hereditary diseases. Image by Cameron Slayden and Nathalie Cary; reprinted with permission from AAAS.

Cloning

Human cloning may refer to "therapeutic cloning," particularly the cloning of embryonic cells to obtain organs for transplantation or for treating injured nerve cells and other health purposes. Human cloning more typically refers to "reproductive cloning," the use of somatic cell nuclear transfer (SCNT) to obtain eggs that could develop into adult individuals.

Human cloning has occasionally been suggested as a way to improve the genetic endowment of mankind, by cloning individuals of great achievement, for example, in sports, music, the arts, science, literature, politics, and the like, or of acknowledged virtue. These suggestions seemingly have never been taken seriously. However, some individuals have expressed a wish, however unrealistic, to be cloned, and some physicians have on occasion advertised that they were ready to carry out the cloning (30). The obstacles and drawbacks are many and insuperable, at least at the present state of knowledge.

Biologists use the term cloning with variable meanings, although all uses imply obtaining copies more or less precise of a biological entity. Three common uses refer to cloning genes, cloning cells, and cloning individuals. Cloning an individual, particularly in the

case of a multicellular organism, such as a plant or an animal, is not strictly possible. The genes of an individual, the genome, can be cloned, but the individual itself cannot be cloned, as it will be made clear below.

Cloning genes or, more generally, cloning DNA segments is routinely done in many genetics and pharmaceutical laboratories throughout the world (12, 31). Technologies for cloning cells in the laboratory are seven decades old and are used for reproducing a particular type of cell, for example a skin or a liver cell, in order to investigate its characteristics.

Individual human cloning occurs naturally in the case of identical twins, when two individuals develop from a single fertilized egg. These twins are called identical, precisely because they are genetically identical to each other.

The sheep Dolly, cloned in July 1996, was the first mammal artificially cloned using an adult cell as the source of the genotype. Frogs and other amphibians were obtained by artificial cloning as early as 50 y earlier (32).

Cloning an animal by SCNT proceeds as follows. First, the genetic information in the egg of a female is removed or neutralized. Somatic (i.e., body) cells are taken from the individual selected to be cloned, and the cell nucleus (where the genetic information is stored) of one cell is transferred with a micropipette into the host oocyte. The egg, so "fertilized," is stimulated to start embryonic development (33).

Can a human individual be cloned? The correct answer is, strictly speaking, no. What is cloned are the genes, not the individual; the genotype, not the phenotype. The technical obstacles are immense even for cloning a human's genotype.

Ian Wilmut, the British scientist who directed the cloning project, succeeded with Dolly only after 270 trials. The rate of success for cloning mammals has notably increased over the years without ever reaching 100%. The animals presently cloned include mice, rats, goats, sheep, cows, pigs, horses, and other mammals. The great majority of pregnancies end in spontaneous abortion (34). Moreover, as Wilmut noted, in many cases, the death of the fetus occurs close to term, with devastating economic, health, and emotional consequences in the case of humans (35).

In mammals, in general, the animals produced by cloning suffer from serious health handicaps, among others, gross obesity, early death, distorted limbs, and dysfunctional immune systems and organs, including liver and kidneys, and other mishaps. Even Dolly had to be euthanized early in 2003, after only 6 y of life, because her health was rapidly decaying, including progressive lung disease and arthritis (35, 36).

The low rate of cloning success may improve in the future. It may be that the organ and other failures of those that reach birth will be corrected by technical advances. Human cloning would still face ethical objections from a majority of concerned people, as well as opposition from diverse religions. Moreover, there remains the limiting consideration asserted earlier: it might be possible to clone a person's genes, but the individual cannot be cloned. The character, personality, and the features other than anatomical and physiological that make up the individual are not precisely determined by the genotype.

The Genotype and the Individual

The genetic makeup of an individual is its genotype. The phenotype refers to what the individual is, which includes not only the individual's external appearance or anatomy, but also its physiology, as well as behavioral predispositions and attributes, encompassing intellectual abilities, moral values, aesthetic preferences, religious values, and, in general, all other behavioral characteristics or features, acquired by experience, imitation, learning, or in any other way throughout the individual's life, from conception to death. The phenotype results from complex networks of interactions between the genes and the environment.

A person's environmental influences begin, importantly, in the mother's womb and continue after birth, through childhood, adolescence, and the whole life. Impacting behavioral experiences are associated with family, friends, schooling, social and political life, readings, aesthetic and religious experiences, and every event in the person's life, whether conscious or not. The genotype of a person has an unlimited number, virtually infinite, of possibilities to be realized, which has been called the genotype's "norm of reaction," only one of which will be the case in a particular individual (37). If an adult person is cloned, the disparate life circumstances experienced many years later would surely result in a very different individual, even if anatomically the individual would resemble the genome's donor at a similar age.

An illustration of environmental effects on the phenotype, and of interactions between the genotype and the environment, is shown in Fig. 2 (38). Three plants of the cinquefoil, *Potentilla glandulosa*, were collected in California—one on the coast at about 100 ft above sea level (Stanford), the second at about 4,600 ft (Mather), and the third in the Alpine zone of the Sierra Nevada at about 10,000 ft above sea level (Timberline). From each plant, three cuttings were obtained in each of several replicated experiments, which were planted in three experimental gardens at different altitudes, the same gardens from which the plants were collected. The division of one plant ensured that all three cuttings planted at different altitudes had the same genotype; that is, they were genetic clones from one another. (*P. glandulosa*, like many other plants, can be reproduced by cuttings, which are genetically identical.)

Comparison of the plants in any row shows how a given genotype gives rise to different phenotypes in different environments. Genetically identical plants (for example, those in the bottom row) may prosper or not, even die, depending on the environmental conditions. Plants from different altitudes are known to be genetically different. Hence, comparison of the plants in any column shows that in a given environment, different genotypes result in different phenotypes. An important inference derived from this experiment is that there is no single genotype that is best in all environments.

The interaction between the genotype and the environment is similarly significant, or even more so, in the case of animals. In one experiment, two strains of rats were selected over many generations; one strain for brightness at finding their way through a maze and the other for dullness (Fig. 3; ref. 39). Selection was done in the bright strain by using the brightest rats of each generation to breed the following generation, and in the dull strain by breeding the dullest rats of every generation. After many generations of selection, the descendant bright rats made only about 120 errors running through the maze, whereas dull rats averaged 165 errors. That is a 40% difference. However, the differences between the strains disappeared when rats of both strains were raised in an unfavorable environment of severe deprivation, where both strains averaged 170 errors. The differences also nearly disappeared when the rats were raised with abundant food and other favorable conditions. In this optimal environment, the dull rats reduced their average number of errors from 165 to 120. As with the cinquefoil plants, we see (*i*) that a given genotype gives rise to different phenotypes in different environments and (*ii*) that the differences in phenotype between two genotypes change from one environment to another—the genotype that is best in one environment may not be best in another.

Cloning Humans?

In the second half of the 20th century, as dramatic advances were taking place in genetic knowledge, as well as in the genetic technology often referred to as "genetic engineering," some utopian proposals were advanced, at least as suggestions that should be explored and considered as possibilities, once the technologies had sufficiently progressed. Some proposals suggested that persons of

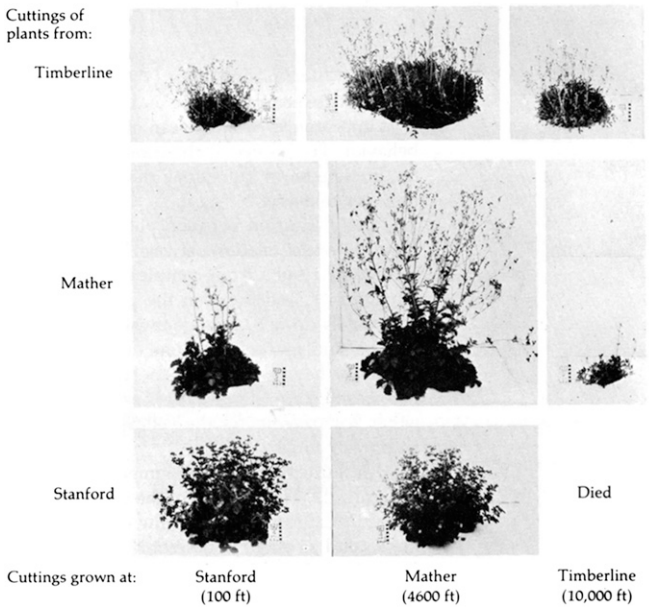

Fig. 2. Interacting effects of the genotype and the environment on the phenotype of the cinquefoil *Pontentilla glandulosa*. Cuttings of plants collected at different altitudes were planted in three different experimental gardens. Plants in the same row are genetically identical because they have been grown from cuttings of a single plant; plants in the same column are genetically different but have been grown in the same experimental garden. Reprinted with permission from ref. 13.

great intellectual or artistic achievement or of great virtue be cloned. If this was accomplished in large numbers, the genetic constitution of mankind would, it was argued, considerably improve.

Such utopian proposals are grossly misguided. It should be apparent that, as stated above, it is not possible to clone a human individual. Seeking to multiply great benefactors of humankind, such as persons of great intelligence or character, we might obtain the likes of Stalin, Hitler, or Bin Laden. As the Nobel Laureate geneticist George W. Beadle asserted many years ago: "Few of us would have advocated preferential multiplication of Hitler's genes. Yet who can say that in a different cultural context Hitler might not have been one of the truly great leaders of men, or that Einstein might not have been a political villain" (8). There is no reason whatsoever to expect that the genomes of individuals with excellent attributes would, when cloned, produce individuals similarly endowed with virtue or intelligence. Identical genomes yield, in different environments, individuals who may be quite different. Environments cannot be reproduced, particularly several decades apart, which would be the case when the genotype of the persons selected because of their eminent achievement might be cloned.

Are there circumstances that would justify cloning a person, because he or she wants it? One might think of a couple unable to have children, or a man or woman who does not want to marry, or of two lesbian lovers who want to have a child with the genotype of one in an ovum of the other, or of other special cases that might come to mind (40). It must be, first, pointed out that the cloning technology has not yet been developed to an extent that would make possible to produce a healthy human individual by cloning. Second, and most important, the individual produced by cloning would be a very different person from the one whose genotype is cloned, as belabored above.

Ethical, social, and religious values will come into play when seeking to decide whether a person might be allowed to be cloned. Most people are likely to disapprove. Indeed, many countries have prohibited human cloning. In 2004, the issue of cloning was raised in several countries where legislatures were also considering whether research on embryonic stem cells should be supported or allowed. The Canadian Parliament on March 12, 2004 passed legislation permitting research with stem cells from embryos under specific conditions, but human cloning was banned, and the sale of sperm and payments to egg donors and surrogate mothers were prohibited. The French Parliament on July 9, 2004 adopted a new bioethics law that allows embryonic stem cell research but considers human cloning a "crime against the human species." Reproductive cloning experiments would be punishable by up to 20 y in prison. Japan's Cabinet Council for Science and Technology Policy voted on July 23, 2004 to adopt policy recommendations that would permit the limited cloning of human embryos for scientific research but not the cloning of individuals. On January 14, 2001, the British government amended the Human Fertilization and Embryology Act of 1990 by allowing embryo research on stem cells and allowing therapeutic cloning. The Human Fertilization and Embryology Act of 2008 explicitly prohibited reproductive cloning but allowed experimental stem cell research for treating diabetes, Parkinson's disease, and Alzheimer's disease (41, 42). On February 3, 2014, the House of Commons voted to legalize a gene therapy technique known as mitochondrial replacement, or three-person in vitro fertilization, in which mitochondria from a donor's egg cell contribute to a couple's embryo (43). In the United States, there are currently no federal laws that ban cloning completely (42). Thirteen states (Arkansas, California, Connecticut, Iowa, Indiana, Massachusetts, Maryland, Michigan, North Dakota, New Jersey, Rhode Island, South Dakota, and Virginia) ban reproductive cloning, and three states (Arizona, Maryland, and Missouri) prohibit use of public funds for research on reproductive cloning (44).

Therapeutic Cloning

Cloning of embryonic cells (stem cells) could have important health applications in organ transplantation, treating injured nerve cells, and otherwise. In addition to SCNT, the method discussed above for cloning individuals, another technique is available, induced pluripotent stem cells (iPSCs), although SCNT has proven

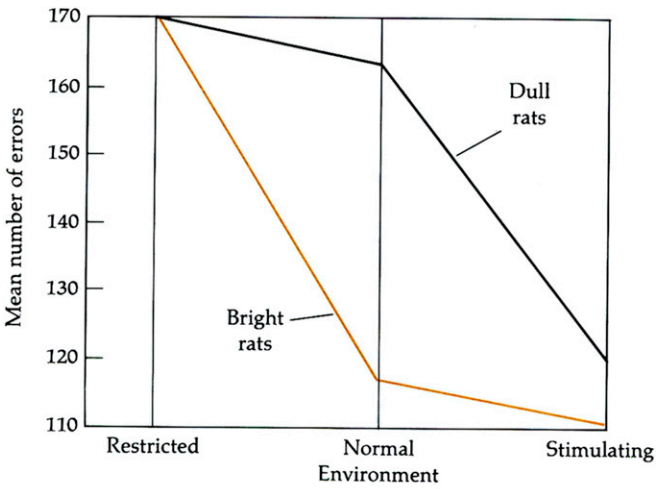

Fig. 3. Results of an experiment with two strains of rats: one selected for brightness and the other for dullness. After many generations of selection, when raised in the same environment in which the selection was practiced (normal), bright rats made about 45 fewer errors than dull rats in the maze used for the tests. However, when the rats were raised in an impoverished (restricted) environment, bright and dull rats made the same number of errors. When raised in an abundant (stimulating) environment, the two strains performed nearly equally well. Reprinted with permission from ref. 13.

to be much more effective and less costly. The objective is to obtain pluripotent stem cells that have the potential to differentiate in any of the three germ layers characteristic of humans and other animals: endoderm (lungs and interior lining of stomach and gastrointestinal tract), ectoderm (nervous systems and epidermal tissues), and mesoderm (muscle, blood, bone, and urogenital tissues). Stem cells, with more limited possibilities than pluripotent cells, can also be used for specific therapeutic purposes (45).

Stem cell therapy consists of cloning embryonic cells to obtain pluripotent or other stem cells that can be used in regenerative medicine, to treat or prevent all sorts of diseases, and for the transplantation of organs. At present, bone marrow transplantation is a widely used form of stem cell therapy; stem blood cells are used in the treatment of sickle cell anemia, a lethal disease when untreated, which is very common in places where malaria is rife because heterozygous individuals are protected against infection by *Plasmodium falciparum*, the agent of malignant malaria. One of the most promising applications of therapeutic cloning is the growth of organs for transplantation, using stem cells that have the genome of the organ recipient. Two major hurdles would be overcome. One is the possibility of immune rejection; the other is the availability of organs from suitable donors. Another regenerative medical application that might be anticipated is the therapeutic growth of nerve cells. There are hundreds of thousands of individuals throughout the world paralyzed from the neck down and confined for life to a wheelchair as a consequence of damage to the spinal cord below the neck, often as a consequence of a car accident or a fall, that interrupts the transmission of nerve activity from the brain to the rest of the body and vice versa. A small growth of nerve cells sufficient to heal the wound in the spinal cord would have enormous health consequences for the wounded persons and for society.

At present, the one gene therapy modification of the embryo that can be practiced is mitochondrial replacement (MR), legalized in the United Kingdom by the House of Commons on February 3, 2014 (43), as mentioned earlier. Mutations in the mitochondrial DNA of about 1 in 6,500 individuals account for a variety of severe and often fatal conditions, including blindness, muscular weakness, and heart failure (46). With MR, the embryo possesses nuclear DNA from the mother and father, as well as mtDNA from a donor female who has healthy mtDNA. However, MR remains technically challenging, with a low rate of success. One complicating issue is that mtDNA replacement is not 100% successful; disease-causing mutant mtDNA persists in the developing embryo and may account for eventual diseases due to heteroplasmy, at least in some tissues. A second issue of concern is that mtDNA disorders often appear late in life. It remains unknown whether the benefits of MR as currently practiced may persist in advanced age.

1. Lordkipanidze D, et al. (2013) A complete skull from Dmanisi, Georgia, and the evolutionary biology of early *Homo*. *Science* 342(6156):326–331.
2. Cela-Conde CJ, Ayala FJ (2007) *Human Evolution. Trails from the Past* (Oxford Univ Press, Oxford, UK).
3. Higham T, et al. (2014) The timing and spatiotemporal patterning of Neanderthal disappearance. *Nature* 512(7514):306–309.
4. Pääbo S (2014) *Neanderthal Man: Search of Lost Genomes* (Basic Books, New York).
5. Ayala FJ (2007) *Darwin's Gift to Science and Religion* (Joseph Henry Press, Washington, DC).
6. Boyd R, Richerson PJ (1985) *Culture and the Evolutionary Process* (Univ of Chicago Press, Chicago).
7. Boyd R, Richerson PJ (2005) *The Origin and Evolution of Cultures* (Oxford Univ Press, Oxford, UK).
8. Ayala FJ (1986) Whither mankind? The choice between a genetic twilight and a moral twilight. *Am Zool* 26(3):895–905.
9. Richerson PJ, Boyd R (2005) *Not by Genes Alone* (Univ of Chicago Press, Chicago).
10. Arias E (2010) United States life tables, 2006. *Natl Vital Stat Rep* 58(21):1–40.
11. Crow JF (1958) Some possibilities for measuring selection intensities in man. *Hum Biol* 30(1):1–13.
12. Lynch M (2007) *The Origins of Genome Architecture* (Sinauer, Sunderland, MA).
13. Ayala FJ (1982) *Population and Evolutionary Genetics. A Primer* (Benjamin/Cummings, Menlo Park, CAa).
14. Harrison GAS, ed (1993) *Human Adaptation* (Oxford Univ Press, Oxford, UK).
15. Mascie-Taylor CGN, ed (1993) *The Anthropology of Disease* (Oxford Univ Press, Oxford, UK).
16. Nesse RM, Williams GC (1994) *Why We Get Sick* (Random House, New York).
17. Bainbridge JW, et al. (2008) Effect of gene therapy on visual function in Leber's congenital amaurosis. *N Engl J Med* 358(21):2231–2239.
18. Cideciyan AV, et al. (2009) Vision 1 year after gene therapy for Leber's congenital amaurosis. *N Engl J Med* 361(7):725–727.
19. Sheridan C (2011) Gene therapy finds its niche. *Nat Biotechnol* 29(2):121–128.
20. Friedmann T, Roblin R (1972) Gene therapy for human genetic disease? *Science* 175(4025):949–955.
21. Wilson EO (2014) *The Meaning of Human Existence* (Liveright, New York).
22. Blaese RM, et al. (1995) T lymphocyte-directed gene therapy for ADA- SCID: Initial trial results after 4 years. *Science* 270(5235):475–480.
23. Abbott A (1992) Gene therapy. Italians first to use stem cells. *Nature* 356(6369):465.
24. Cavazzana-Calvo M, Thrasher A, Mavilio F (2004) The future of gene therapy. *Nature* 427(6977):779–781.
25. Fischer A, Hacein-Bey-Abina S, Cavazzana-Calvo M (2010) 20 years of gene therapy for SCID. *Nat Immunol* 11(6):457–460.
26. Cartier N, Aubourg P (2010) Hematopoietic stem cell transplantation and hematopoietic stem cell gene therapy in X-linked adrenoleukodystrophy. *Brain Pathol* 20(4): 857–862.
27. LeWitt PA, et al. (2011) AAV2-GAD gene therapy for advanced Parkinson's disease: A double-blind, sham-surgery controlled, randomised trial. *Lancet Neurol* 10(4): 309–319.
28. Herper M (2014) Gene therapy's big comeback. *Forbes*. Available at www.forbes.com/sites/matthewherper/2014/03/26/once-seen-as-too-scary-editing-peoples-genes-with-viruses-makes-a-618-million-comeback/. Accessed March 1, 2015.
29. Muller HJ (1950) Our load of mutations. *Am J Hum Genet* 2(2):111–176.
30. Writer S (2001) In the news: Antinori and Zavos. *Times Higher Education*. Available at www.timeshighereducation.co.uk/164313.article. Accessed March 1, 2015.
31. Jobling MA, Hurles ME, Tyler-Smith C (2004) *Human Evolutionary Genetics* (Origins, Peoples & Disease, Garland Science, NY).
32. King TJ (1996) Nuclear transplantation in amphibia. *Methods in Cell Physiology*, ed Prescott DM (Academic Press, New York), Vol 2, pp 1–36.
33. McLaren A (2000) Cloning: Pathways to a pluripotent future. *Science* 288(5472): 1775–1780.
34. Jabr F (2013) Will cloning ever save endangered animals? *Sci Am*. Available at www.scientificamerican.com/article/cloning-endangered-animals/. Accessed March 1, 2015.
35. Highfield R (2007) Dolly creator Prof. Ian Wilmut shuns cloning. *Daily Telegraph*. Available at www.telegraph.co.uk/news/science/science-news/3314696/Dolly-creator-Prof-Ian-Wilmut-shuns-cloning.html. Accessed March 1, 2015.
36. Shiels PG, et al. (1999) Analysis of telomere lengths in cloned sheep. *Nature* 399(6734): 316–317.
37. Ayala FJ, Kiger JA (1984) *Modern Genetics* (Benjamin/Cummings, Menlo Park, CA), 2nd Ed.
38. Claussen J, Keck DD, Hiesey WM (1940) *Experimental Studies on the Nature of Species. I. The Effect of Varied Environment on Western North American Plants. Carnegie Institution of Washington Publication 520* (Carnegie Institution of Washington, Washington, DC).
39. Cooper RM, Zubek JP (1958) Effects of enriched and restricted early environments on the learning ability of bright and dull rats. *Can J Psychol* 12(3):159–164.
40. Kitcher P (1996) *The Lives to Come. The Genetic Revolution and Human Possibilities* (Simon & Schuster, New York).
41. Writer S (2008) MPs support embryology proposals. *BBC News Online*. Available at news.bbc.co.uk/2/hi/uk_news/politics/7682722.stm. Accessed March 1, 2015.
42. UK Statute Law Database (2001) Text of the human fertilisation and embryology (research purposes) regulations 2001 (no. 188). Available at www.legislation.gov.uk/uksi/2001/188/contents/made. Accessed March 1, 2015.
43. Callaway E (2015) World hails embryo vote. *Nature* 518(7538):145–146.
44. NCSL (2008) Human cloning laws. National Conference of State Legislatures (NCSL). Available at www.ncsl.org/research/health/human-cloning-laws.aspx. Accessed March 1, 2015.
45. Kfoury C (2007) Therapeutic cloning: Promises and issues. *McGill J Med* 10(2):112–120.
46. Gemmel N, Wolff JN (2015) Mitochondrial replacement therapy: Cautiously replace the master manipulator [published online ahead of print February 27, 2015]. *Bioessays*, 10.1002/bies.201500008.