THE FATEFUL CODE

Genes and Human Destiny

Every day seems to bring fresh news of astonishing discoveries on the frontiers of genetic research. Genes "for" homosexuality, alcoholism, and dozens of diseases. A dazzling array of genetically engineered medicines and goods, from cancer-fighting drugs to coffee plants that yield caffeine-free beans. Now, with the launching of the $3-billion U.S. Human Genome Project, comes the prospect of unlocking the last secrets of the gene and, some critics assert, the dread possibility of discoveries that will allow scientists to create a super-race. Yet genetic research is surrounded by misunderstanding. Many supposed "breakthroughs" are only beginnings, and some have little more substance than cold fusion. Our authors explore the science behind the headlines, assessing the specter of eugenics and pondering the impact of genetic research on our understanding of human nature itself.

THE DOUBLE-EDGED HELIX

by Joel L. Swerdlow

Over the centuries, medical progress has eased human suffering and prolonged human lives without asking much in return. Vaccinations, antibiotics, and open-heart surgery, to name a few advances, have not generally posed significant moral problems. Today, however, the dawn of an era of gene-based medicine holds out tantalizing promises that carry with them a growing list of new and often disturbing choices for individuals, for physicians and researchers, and for society at large.

Some dilemmas are distant, including the possibility that growing mastery over genes will give us unprecedented power over our children's genetic makeup. Others are upon us already, namely the question of who has a right to possess genetic information about individuals' susceptibility to certain diseases. Some of the more urgent conundrums arise because science is still at an awkward "halfway" point: It offers significant new knowledge about genes but few ways to respond.

One of these halfway points is the discovery of the "genetic marker" for Huntington's disease, an inherited nerve disorder that appears at around age 40 and slowly kills the brain. No one knows why, and no treatment exists. The responsible gene is dominant. When one parent has Huntington's, each offspring has a 50-50 chance of developing it. Before the discovery of the marker, children of such parents could only wait to see if they would die. One of these is Nancy Wexler, a Columbia University psychologist whose mother died of Huntington's. Beginning in 1979, she recruited some 2,000 Venezuelan donors—all of them descendants of a single 19th-century woman who suffered from the disease—whose pedigree and blood samples made possible in 1983 the discovery of the genetic marker for Huntington's. If one of a person's parents had Huntington's and that person's DNA includes this marker, he or she likely will develop the disease.

Wexler was elated when her colleagues discovered the Huntington's marker. But nine years later, researchers are no nearer to developing anything that prevents, treats, or cures Huntington's. That creates terrible dilemmas for people at risk. Imagine a man whose father died of Huntington's. To find that he does not carry the marker liberates him. But if he finds that he does have the marker, he is compelled to count the days until horror and death hit. Faced with this choice, less than 15 percent of those at risk have decided to undergo genetic screening. Wexler herself will not reveal whether she has been screened.

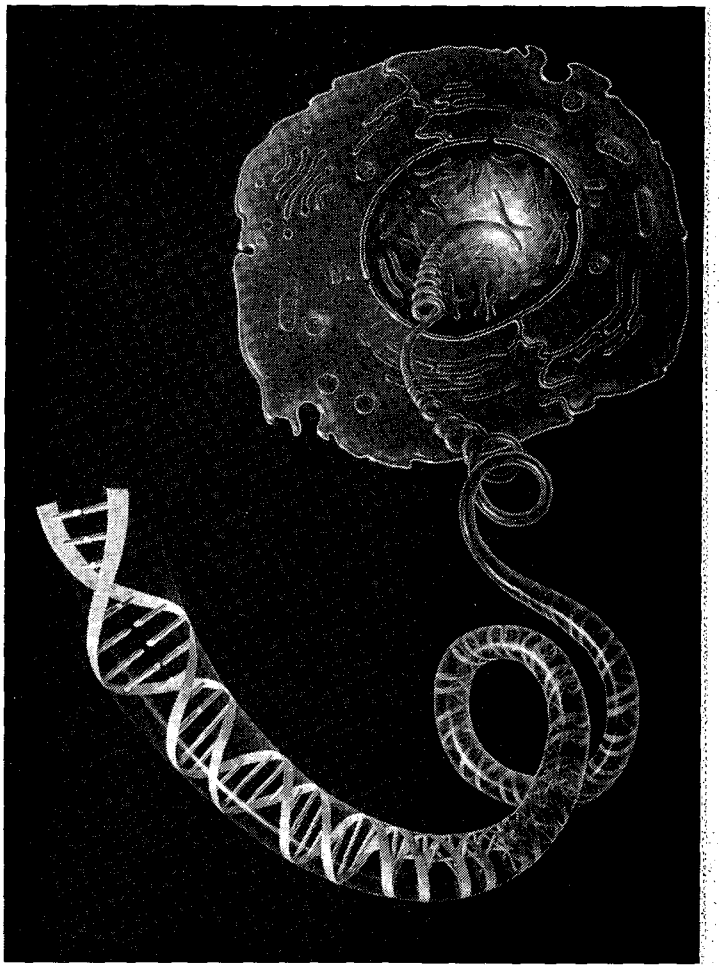
The genetic revolution that is gathering force today, says science journalist Harold Schmeck, can be understood as "scientists' growing ability to read and write in the language of the gene." Modern scientific un-

derstanding of genetics dates from 1866, when an Augustinian monk named Gregor Mendel, who had been experimenting with pea plants in Austria, published a paper laying out the basic laws of inheritance. Mendel made his discovery without knowing about genes or chromosomes, and it was only in 1900, after scientists had, among other things, observed chromosomes through a microscope, that his work was rediscovered.

Advances—such as the recognition by George W. Beadle and Edward L. Tatum in 1941 that the function of genes is to create enzymes and proteins—built steadily. The big breakthrough came in 1953, when James Watson and Francis Crick at Cambridge University deciphered the structure of deoxyribonucleic acid (DNA), the molecule that carries genetic information. Each cell has six to nine feet of DNA coiled on 23 pairs of chromosomes. The DNA, in the now familiar shape of a double helix, consists of two strands of nucleotides, which are made of sugar, phosphate, and one of four different bases. The strands are joined by either of two pairs of bases: adenine (A) and thymine (T), or cytosine (C) and guanine (G). That base-pair rule means that when cells (and thus strands of DNA) divide, each strand can make a copy of its former partner.

Every genetic instruction is encoded through the linear order of the four bases on a segment of DNA, much as computer information is stored in a binary code of 1's and 0's. In 1959, Crick and others found the intermediary that carries each instruction from the DNA to the ribosomes, where the instruction is translated into action through the creation of proteins. This messenger is a chemical cousin of DNA called ribonucleic acid, or RNA.

That, of course, is only the beginning of the mystery, for each chromosome has as many as 300 million base pairs. In order to understand the human genome (the total of all genetic information), scientists will have to decipher some three billion human base pairs. Listing them would fill 13 sets of the *Encyclopedia Britannica*. Most of the genes bearing specific instructions vary in length from about 100 to 30,000 base pairs, and even now scientists are not sure how many human genes there are. Estimates generally



A double helix of DNA, joined at intervals by base pairs, uncoils from the nucleus of a cell in this artist's conception.

range from 50,000 to 100,000. So far, researchers have "mapped" the location of nearly 2,000 genes (up from 579 in 1981) and have identified some 4,000 diseases caused by single-gene defects. Most of these diseases are relatively rare, such as Duchenne muscular dystrophy, retinoblastoma, neurofibromatosis, and one form of Alzheimer's. Most common diseases that have genetic roots probably will be traced to more than one gene.

During the 1960s and '70s, scientists realized that variations in DNA may be associated with diseases and that "markers," patterns of base pairs, appear on the same place of the same chromosome of virtually everyone. A number of technological advances—in microscopy and related areas—dramatically increased researchers' ability to isolate genes and tinker with various genetic components. Yet most of these experiments were performed on bacteria and other simple organisms. Turning their attention to more complex organisms in the late 1960s, scientists discovered that similar methods could still be used. In 1973, these techniques were given the name "recombinant DNA"—popularly known as gene splicing or, more ominously, genetic engineering.

Recombinant DNA involves snipping sections of the DNA molecule from a complex organism using restriction enzymes and transplanting the snips into host bacteria or yeast cells. (The use of yeast cells is actually a more recent innovation, giving rise to yet another of the acronyms so beloved by scientists, YACs, for yeast artificial chromosomes.) The host cells then multiply normally, creating many new "clones" of the transplanted DNA at the same time. These clones contain anywhere from a few hundred to one million base pairs.

Clones created by this method (and others) have a variety of uses. Applying other techniques, for example, scientists found that they could transplant and "turn on" some genes, getting them to produce vital biochemical substances such as human growth hormone and insulin. More significantly, perhaps, cloning meant that researchers could create large "libraries" of DNA fragments for further manipulation or study in the laboratory.

By the mid-1980s, these and other technological advances made the prospect of exploring the entire human genome seem feasible. One of the most important developments was the 1983 discovery by Wexler and her collaborators of the genetic marker for Huntington's disease. Finding such a genetic malfunction is a monumental enterprise, somewhat analogous to locating a broken pipe in a house somewhere on Earth (the cell). You narrow your search first to the United States (a particular chromosome) and then to Pennsylvania (chromosome fragment). Finally you focus on Philadelphia (gene) and begin walking block-by-block looking for signs of the leak. Eventually you get close enough to search each house (nucleotide base pairs). The "leak" is an incorrect nucleotide.

Wexler and her colleagues set out in search of the gene in 1979. Using restriction enzymes, which snip DNA strands at particular locations, James Gusella, Wexler's collaborator at Massachusetts General Hospital, chopped up the DNA from the blood samples she supplied. The fragments were separated by size, using a process called gel electrophoresis. Then the hunt began. The idea was to identify segments of DNA that were different in people with Huntington's. Gusella took advantage of the fact that the segments created by

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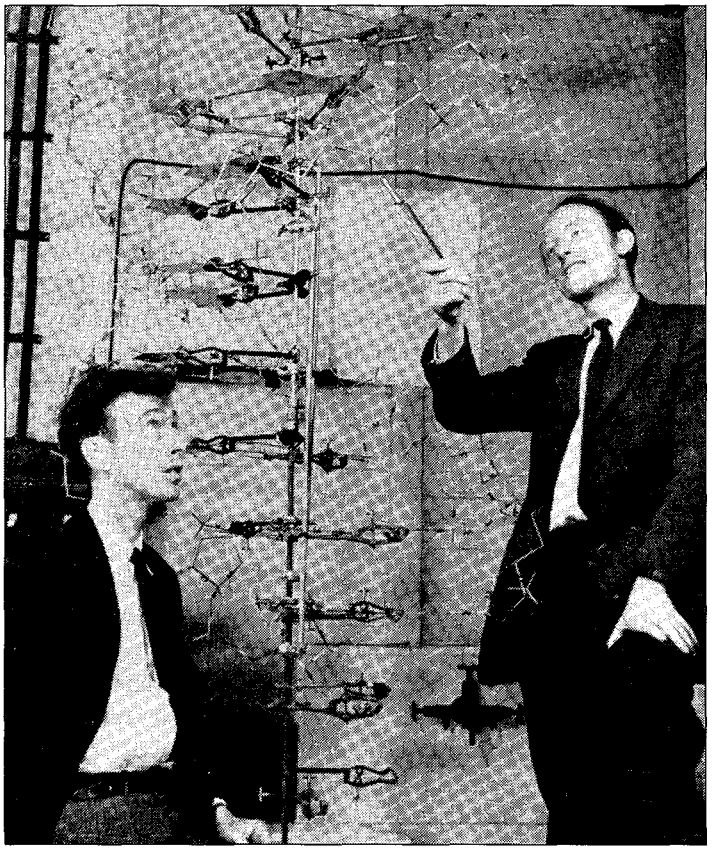
restriction enzymes vary from person to person, resulting in what are called restriction fragment length polymorphisms (RFLPs). He created radioactive RFLP "probes" and added them to the chopped up DNA. The probes then bonded to their complementary segments of DNA and lit up in a banded pattern. Performing this exercise on many samples, Gusella could then compare them to see if all those from people with Huntington's had a pattern of bands distinct from all those without the disease. Still, this was the equivalent of the proverbial search for a needle in a haystack. It could have required the development of thousands of different RFLPs and thousands of tedious tests before stumbling upon the proper segment. But Gusella got lucky. With one of his very first probes, he discovered the variation.

Because *all* of the DNA in each sample had been chopped up, he still did not know which chromosome the culprit snip appeared on. Further laboratory and computer work determined that it was on chromosome 4. The gene for Huntington's disease had been "mapped"—it was within a mere four million base pairs of one end of chromosome 4—but still not precisely located. Indeed, it is a measure of the difficulty of genetic research that, nine years later, researchers still have not found the Huntington's gene. They are, to return to the analogy of the search, still only in Pennsylvania. What Gusella, Wexler, and their colleagues had shown, however, was that RFLP mapping, once dismissed as a fantasy, was feasible.

This and a rapid succession of other developments gave rise to what may be described as a Manhattan Project mentality. The prospect of mapping and sequencing the entire human genome, long a vague dream of a few scientists, now seemed a real possibility. Several leaders of the scientific community, including Nobel laureate Renato Dulbecco, Harvard's Walter Gilbert, and Robert Sinsheimer, a scientist-turned-university administrator, called for a crash program. In Washington, the U.S. Department of Energy (DOE) seized upon the idea in 1986, but its leadership was almost immediately challenged by the National Institutes of Health (NIH). In 1987, Congress, encouraged in part by the prospect of building an insurmountable U.S. lead in the emerging biotechnology industry, gave the two competing agencies $29 million. But many issues were still unresolved.

Some biologists feared the encroachment of bureaucratized Big Science, previously restricted to particle physics and a few other fields. "Many of us oppose brute force sequencing of the human genome because we believe it is an inefficient use of scarce research dollars," one researcher wrote in a letter to *Science*. "[B]iomedical research dollars are generally more efficiently spent on investigator-initiated research. We believe that innovation from scientists in the field produces better science than do narrowly targeted, top-down big science projects."

Defenders of the approach replied that costs of piecemeal research are higher and that a human genome project would stimulate technological innovations that would spare even the independent-minded investigator a great deal of tedious and time-consuming labor in the laboratory and speed the pace of research. Since then, researchers have pointed out that the discovery of the gene that causes fragile X syndrome—the most frequent cause of inherited mental retardation—came roughly five years ahead of schedule because of the Human Genome Project. Some 5,000 babies are born every year in the United States with fragile X syndrome. Minimal health-care costs for each are $100,000. If science can



James Watson (left) and Francis Crick show off the 1953 model of a DNA molecule for which they were later awarded a Nobel Prize.

develop a treatment or cure—admittedly, a big "if"—this discovery alone could allow the Project to pay for itself.

But there was (and continues to be) much disagreement about the need to sequence all of the DNA, since 90–95 percent of it consists of "introns" that do not "code" for genes and may be useless litter left over from evolution. "[T]his vast genetic desert holds little promise of yielding many gems," says Robert A. Weinberg, of the Whitehead Institute for Biomedical Research. "As more and more genes are isolated and sequenced, the argument that this junk DNA will yield great surprises becomes less and less persuasive." Nobel Prize-winning biochemist Paul Berg, by contrast, says, "There is already clear evidence that specific sequences in introns and in intergenic [noncoding] regions constitute important regulatory signals.... Are we prepared to dismiss the likelihood of surprises...?"

At a deeper level, there has been a fundamental philosophical disagreement. James Watson argues that studying genes "will provide the ultimate answers to the chemical underpinnings of human existence." Opponents such as Harvard microbiologist Jon Beckwith believe that such views, magnified by the news media, "promote the conception that genetics is all-explanatory," "reinforce a distorted perception of the basis of the human condition," and devalue other biological work.

These larger differences will not likely disappear soon, but in 1988 a committee of the National Research Council that included several critics of Big Biology (such as David Botstein, one of the inventors of RFLP mapping) recommended a 15-year project carried out at 10 major research centers around the country and costing some $200 million annually. It was not the kind of crash Big Science effort some of these critics had feared, and funds were not merely to be shifted from other areas of biomedical research to pay for it.

At the behest of Congress, the two competing bureaucracies reached agreement in 1988. The NIH will focus on mapping, the Energy Department on sequencing. Watson, named to lead the NIH program, has

become the de facto head of what is loosely called the U.S. Human Genome Project. At a projected $3 billion over the next 15 years, the U.S. effort dwarfs those of Japan and Europe.

The project's first priority is to create rough maps of the human genome, while working to improve sequencing technology. Phase two, beginning after 10 years, is to determine the exact sequences of the three billion human nucleotides. Sequencing has become fairly routine, but it is tedious and expensive. ("Virtually any monkey can do it," Watson scoffed last fall when an NIH official announced plans to seek patents for sequences.) With today's technology, it would take several centuries to "read" the entire genome. But a proposed DNA computer chip might analyze sequence data 100 times faster than is now possible.

The challenge of the 21st century will be to interpret the cornucopia of raw information produced by the project and to determine how to make use of it. In a sense, the project will provide only the infrastructure for the research of the future. Genes will still need to be located, their functions understood. Knowing that a base sequence is GGATCC, for example, is not enough to reveal what function is served by the protein it encodes. Scientists will need to explore the complex *interplay* among genes that influence or produce human traits and diseases. And they will need to discover how one fetal cell's DNA is told to multiply into brain cells and another's into bone cells.

Even so, practical applications of genetic research already are permeating medicine. On September 14, 1990, for example, Dr. W. French Anderson and two colleagues at the National Institutes of Health in Bethesda, Maryland, made medical history by performing the first sanctioned "gene therapy" on a human being. A *New York Times Magazine* profile noted that Anderson needed political skills nearly as great as his medical ones to win approval from the bureaucracy and Congress. The patient was a four-year-old girl who suffered from adenosine deaminase (ADA) deficiency, an inborn inability to produce an enzyme essential to the immune system. Anderson and his colleagues inserted the gene for ADA into a retrovirus that had been stripped of most of its own genetic material. When mixed with a sample of the girl's own white blood cells, the retrovirus went about its normal business of penetrating the nucleus of each cell, carrying with it the ADA gene.* On that September day, the process reached its historic if undramatic culmination when the girl's "improved" white blood cells were returned to her by transfusion. Since then, she has continued to receive the controversial therapy, and other researchers have won permission to begin similar treatments for cancer, hemophilia, and cystic fibrosis.

The greatest practical benefits from genetic research so far have come in the form of "biotech" drugs. They have spawned a $12 billion industry—dominated by American firms such as Amgen, Genzyme, and Immunex—that is expected to grow to $40–60 billion by the end of the decade. Many biotech drugs are substances normally produced in the human body that are synthesized in the laboratory by taking the relevant genes and inserting them into yeast or bacteria cells, then harvesting the natural substances they create. Tens of millions of patients now use these genetic products to combat afflictions such as diabetes, hepatitis, and anemia. The drugs include not only such familiar substances as

*Cell transplantation is a related procedure, cruder in that entire cells are used to correct for genetic defects. For example, researchers can obtain insulin-producing "islet" cells from dead donors and place them in the livers of patients unable to produce their own insulin.

insulin but epogen, which stimulates the production of red blood cells and thus allows kidney dialysis patients to avoid transfusions, and neupogen, which increases the production of white blood cells in cancer patients undergoing chemotherapy.

Finally, and most significantly, genetic research has made possible "predictive," presymptomatic medicine. In 1991, for example, researchers discovered a gene responsible for a rare colon cancer. Those with a family history of the disease can be tested for the gene; if they carry it, they can get regular colonoscopies and surgeons can act at the first sign of trouble. However, most predictive medicine lies in the future. A genetic early warning, for example, may some day allow physicians to intervene against juvenile onset diabetes, a disease that afflicts more than one million Americans. By the time it is diagnosed—usually after the appearance of symptoms such as fatigue—most of the victim's insulin-producing islet cells are dead and the patient must begin daily insulin injections.

As in the case of Huntington's disease, however, locating a gene (or marker) and finding a response are two different matters. Researchers discovered dozens of disease-causing genes in the 1970s and '80s without finding the means to prevent or cure the diseases. "We need," says University of California geneticist Paul Billings, "a new physiological revolution. We need new insights and approaches. Until this happens, work with genes can carry us only so far."

Knowledge from the frontiers of genetic research will increasingly pose difficult problems for policymakers and for society at large. Should certain forms of genetic screening be required? Should others be barred or restricted? Most states already require the screening of newborn babies for biochemical disorders such as phenylketonuria (PKU), a hereditary enzyme deficiency that causes mental retardation but which can be offset by a special diet. Indeed, because of other nongenetic medical advances, the list of required tests may soon extend later into childhood. Some state legislatures are considering laws that require the testing of all children at age one or two for lead poisoning. Such mandatory screening arouses little opposition, largely because it is easy, inexpensive, and effective.

But consider the case of cystic fibrosis, the most common inherited fatal disease of children and young people in the United States. Roughly five in 100 Caucasian Americans—about 12 million people—carry a responsible gene. Since it is recessive, such "carriers" are not affected. If two carriers conceive a child, however, it has a one-in-four chance of developing the disease. In the late 1980s, a test was developed to identify carriers. However, results can be ambiguous, in part because more than 100 known mutations of the gene cause cystic fibrosis. The *New York Times* reports, however, that screening for cystic fibrosis is "quietly creeping into clinical practice." The driving force is physicians' fear of malpractice or "wrongful life" lawsuits. To screen all possible carriers in the United States using current technology would cost billions of dollars every year and would provide limited benefits. To forego screening, however, may require more discipline and understanding than most couples can muster. Must the state set limits?

Some genetic discoveries create moral dilemmas. Each year, about 300,000 pregnant women in America seek fetal tests for certain inherited diseases. In some cases experimental treatment of the fetus through surgery or transfusion is possible if an "abnormality" is found. But usually the options are to continue the pregnancy without treatment or to abort the fetus. Many people choose abortions. Since a fetal test

for Tay-Sachs—a fatal neurodegenerative disease—became available in the early 1970s, the number of children born with Tay-Sachs has declined by 90 percent.

Screening, however, does not always encourage abortion. It can allow couples who have had one genetically abnormal child to feel free to conceive another, knowing that a fetal screening will reveal any problems. Yet fetal screening still makes many ethicists and physicians uncomfortable. In Russia, for example, the medical literature shows that a large number of abortions have occurred because screening has revealed that fetuses *might* have the gene for juvenile-onset diabetes. "I don't know if a 20 percent disposition to diabetes is a disease or an abnormality," says Arthur Caplan, director of the Center for Biomedical Ethics at the University of Minnesota. "I'm certainly not sure whether it morally justifies anyone aborting a fetus with that genetic profile. We haven't thought very much yet about how to draw that line between what is a disease and what isn't."

Moreover, many people seem willing to abuse prenatal choices. Demographers have concluded that 100 million Asian females are "missing" from the total population, most presumably aborted because their parents wanted sons. As researchers discover the genetic components of intelligence, will parents abort fetuses lacking Ivy League genes? Will they practice prenatal "heightism," aborting some male fetuses because they will not grow tall enough?

"At what point," asks biotechnology critic Jeremy Rifkin, "do we move from trying to cure horrible genetic diseases to trying to enhance genetic traits?" Despite some vocal dissent in professional journals, the scientific and medical communities have made work on human germ (sperm and egg) cells taboo, but this self-imposed limitation seems destined to end. Experiments with plant and animal germ cells offer enticing prospects—such as no-caffeine coffee beans and "natural" low-fat cow's milk—while doing no known harm. Advocates of germ-cell research point out that physicians already alter eggs or sperm when exposing cancer patients to some forms of radiation and drugs. And finally the ban on germ-cell research forces us to reexamine our notions of nature itself. Is it "natural" to get sick? Isn't medicine constantly fighting nature?

What if your physician said, "You have a family history of heart disease. I can offer a painless and safe injection that will correct this defect in your reproductive cells and guarantee that your children and every descendant thereafter will have a significantly reduced chance of heart disease." Your doctor would explain possible side effects. "It is not clear-cut," the experts would explain. "Gene defects, including those in recessive genes, may do unknown things or defend the body in undiscovered ways, just as the gene for sickle cell anemia offers protection against malaria." Yet it is nevertheless hard to imagine people saying no to such an offer.

While the dilemmas of genetic research give many reasons to pause and reflect, they do not justify slowing or stopping the research itself. In many cases, the best way to eliminate dilemmas—and protect human life—is to push back genetic frontiers. Admittedly, there are risks involved. The more we master genes, the more options—many of them morally questionable—we will have. But making choices, after all, is what being human is all about.