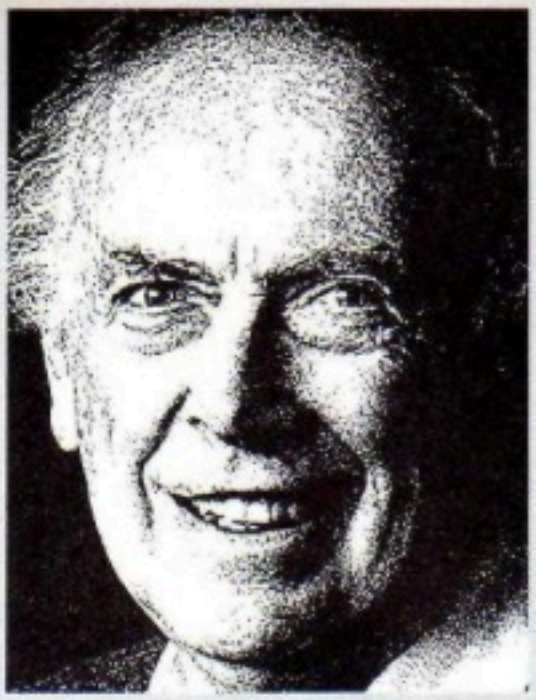

FIRST WORD

By James D. Watson

Drugs may be developed by researchers to correct deficiencies within genes that cause genetic errors, and perhaps defective genes may someday be replaced by healthy ones.

When the United States declared its independence from England in 1776, most maps of North America did not include California, now one of the most populous, diverse, and wealthy states in the nation. Only after the Civil War were California and the American West carefully and systematically mapped out. Expeditions and surveys laid the foundation for renewed exploration of the vast resources available to Americans in the great West.

As the Nineties begin, we are poised to mount a similar effort of even greater importance—to construct the genetic map of humans; to chart the mysteries encoded in the 50,000 to 100,000 genes that make up our bodies.

The human genome represents all genetic material that composes a living person. The chemical composition of this material consists entirely of DNA (deoxyribonucleic acid), the hereditary molecule arranged into working units called genes. Mapping the genome consists of locating every gene on the 23 pairs of our chromosomes squeezed into the nucleus of every cell and sequencing the 3 billion DNA subunits that make up each gene.

The Human Genome Project hatched out of passionate debates during the past several years. The success of the project is a shared commitment among Congress, the National Institutes of Health, the U.S. Department of Energy, and many foreign governments. To mediate the logistics of this large international cooperation, the Human Genome Organization was founded. The expected cost of this extensive biological operation is $3 billion ($1 for every subunit in the DNA chain) over the next 15 years. Unlike other federally funded megaprojects, such as the Apollo moon program, the benefits will begin as soon as data start coming in. We won't have to wait for the completion of the genome to reap the benefits.

This is indeed an expensive endeavor, but the rewards from mapping the genome will be widespread. By defining the structure of DNA, researchers will be able to identify inherited patterns or specific markers on the DNA strand that indicate the source of hereditary diseases. Many of the disorders that dominate our world, such as heart disease, cancer, arthritis, alcoholism, and mental illness, may be caused by genetic abnormalities.

As we analyze the information hidden within the chemical composition of every gene in the human body, the role of medicine will shift from treatment to prevention. For instance, genetic analysis of a newborn may be used to screen for a wide range of genetic disorders. Whenever a defect is found, the child may be protected from illness by the proper diet or by avoiding environmental hazards. Mapping the human genome will also give doctors the tools to test adults for vulnerability to certain diseases before symptoms appear. And eventually drugs may be developed to correct deficiencies within genes that cause genetic errors, and perhaps defective genes may someday be replaced by healthy ones.

In order to fish a single gene out of the sea of genetic material in the body's cells, however, the pioneers exploring the genetic frontier must first push the limits of existing technology. New methods of automation must be cultivated before we can fulfill the goals of the genome project. These technological improvements (primarily advances in engineering) are already being created. A new technology that promises to help interpret data gathered from sequencing will scan the chemical composition of sequenced DNA and pick up patterns that will indicate common genetic functions.

The venture to map the human genome, however, is not without its dangers. We have already witnessed the violent abuse of genetics in the name of eugenics and racial hygiene (the hideous genocide of Jews in Nazi Germany) earlier in this century. The eugenics movement was initiated in the Twenties in Britain and the United States, where its supporters attempted to alter the human stock by controlled breeding through sterilization and laws to prevent racial intermarriages.

The shadows of past abuses loom in the background of genetic research. We can prevent such atrocities from recurring if scientists, doctors, and society at large refuse to cede control of genetic discoveries to those who would misuse them. And one day laws must be passed to protect individuals from harm that might occur from violation of medical confidentiality (between patients and their physicians), resulting from genetic profiles.

We are far more than our genes, but understanding our genes is extraordinarily important. How else can we understand what transforms a normal cell into one that indulges in unregulated growth to become a cancer? How else can we combat Alzheimer's disease, arthritis, or disorders of immunity that result more from "the enemies within" than from infections arising from external sources? The fruits of our labors will be masses of information about the most important set of instructions we can ever study—the human genome. The resulting mountain of knowledge will be mined for centuries, as we strive to conquer disease.

James D. Watson, a pioneer in genetics, received the Nobel prize in medicine in 1962 for codiscovering the structure of DNA. Today he has a new challenge as director of the Human Genome Project.

The Genetic Frontier

James D. Watson

When the United States declared their independence from England in 1776, most maps of North America did not include California, now one of the most populous, diverse, and wealthy states in the nation. The American West was systematically mapped only in the period preceding the Civil War. The western expeditions and surveys, particularly the U.S. Geological Survey under the direction of John Wesley Powell, laid the foundation for the second opening of the American West. As the 1990s begin, we are poised to mount a similar effort of even greater importance — to construct the genetic map of human beings.

The map will in fact be several interlinked by distinct maps of the 24 human chromosomes (22 pairs of nonsex chromosomes and the X and Y sex chromosomes). One kind of map will correlate patterns of inheritance in families with markers on human DNA. This kind of map — a genetic linkage map — can be used to locate genes that cause specific human diseases or that code for important physiological processes. Another kind of map is called a physical map, and it will specify distances between DNA markers by the number of chemical subunits separating them. The most useful kind if physical map will cover large expanses of the human chromosomes with DNA that is already copied and available in cloned bacteria or yeast. The sequence of chemical subunits that make up DNA, the nucleotide sequence, is the ultimate objective of all this work. The information encoded in DNA is stored in the order of these nucleotides along the DNA, much as information is stored in the order of 1's and 0's at specific locations in computer memory.

Scientists have hatched a plan for the Human Genome Project over the past half decade. Robert Sinsheimer, Renato Dulbecco, and Charles DeLisi are not household names, but their vision of a dedicated research program will earn them a place in the history of science. Sinsheimer called the first meeting to discuss a large scale approach to the study of human DNA in 1985. DeLisi independently got the US Department of Energy moving. The National Institutes of Health then followed suit. These two government agencies have now jointly planned a concerted research

effort that should continue into the next century. Dulbecco was among the first in molecular biology to propose a focused effort to elucidate the detailed structure of human DNA. He convinced the Italian government to begin support of pilot research in the area in 1987. Now, the USSR, the United Kingdom, and Japan have joined the US and Italy. Other nations should soon add their voices to the chorus.

The process of beginning the project has been noisy, almost chaotic at times. But the project is far stronger because of the redefinition of its goals that emerged from many passionate debates. It is now a shared commitment among Congress, science agencies, and many foreign governments. The Human Genome Organization was founded to mediate the logistics of this large international project, and much hangs on its future success.

Pioneers exploring the genetic frontier will push the limits of technology. They must create new methods to fish a single gene out of the sea of genetic material in the body's cells, and they must fabricate complex parallel array microchips to make sense of deluge of genetic data. The fruits of our labors will be masses of information about the instruction set for creating a human being -- the human genome -- the most important set of instructions we can ever study. The resulting mountain of information will be mined for centuries, as we strive to understand ourselves and conquer disease.

The venture is not without its dangers. We have already witnessed the violent abuse of genetics for political purposes in the name of eugenics and racial hygiene earlier in this century. Several countries still have eugenics statutes, and the shadows of past abuses constantly loom in the background of genetics research. The future of genetics can be bright only if scientists, doctors, and society at large keep it from becoming tarnished again. We can, because we have learned. Genetic information can be turned to cause harm, let there be no doubt. But we can stop that from happening if we remain vigilant and refuse to cede control of the technologies to those who would misuse them. Laws must be passed that protect individuals from harm that might come

from violations of confidentiality, and efforts to enact coercive social policies based on arguments from genetics must be vigorously opposed, first of all by scientists but also by all of society.

The benefits vastly outweigh the risks. Genetics is the most fundamental of biological sciences. DNA is the informational hub that copies instructions to the next generation and at the same time translates it to instructions that govern all cellular functions. We are far more than our genes, but understanding our genes is extraordinarily important.

How else can we understand what transforms a normal cell into one that indulges in unregulated growth to become a cancer? How else can we begin to combat Alzheimer's disease, arthritis, disorders of immunity, and other chronic diseases that result more from "the enemies within" than from infections arising from external sources. Having the genetic maps we will construct in the Human Genome Project will not make these ills go away, but they will go away faster for our efforts. That is obviously good.