DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Statement of the Director
National Center for Human Genome Research

Mr. Chairman, my testimony today describes a landmark turning point in human genetics research at the National Institutes of Health, as well as progress in the Human Genome Project only the most ambitious imaginations would have believed possible even two years ago. I am honored to appear before you as the new Director of the National Center for Human Genome Research and look forward to guiding this critical and path-breaking organization, which I believe will change the face of medical practice in the years to come. I am particularly grateful for the past able leadership of Dr. James Watson and, in recent months, Dr. Michael Gottesman, who guided the NCHGR program through its critical early stages and who have made it possible for me to take over a successful and extraordinarily well-managed organization.

My appointment brings with it not only a new director for NCHGR but a new direction for molecular medicine at the NIH. Two months ago, NCHGR established a Division of Intramural Research on the NIH campus, which will enhance the NIH community's ability to apply Human Genome Project technologies to the vast number of genetic diseases now under study at the various NIH Institutes. While gene studies are a component of nearly all intramural science at NIH, no central program currently coordinates this cross-cutting research. As the hub of expertise in genome technology, NCHGR's new intramural program, with a request level of $24,840,000 in FY 1994, will provide needed infrastructure to genetic and molecular studies of an array of important genetic diseases, and even common complex diseases, such as

diabetes, cancer, hypertension, heart disease, and mental illness. To enable the rapid and efficient discovery of disease genes, the new laboratory will offer expertise in genetic analysis of families, statistical analysis, as well as various techniques in chromosome mapping, marker development, and DNA analysis. Research in vector technology and human applications of gene therapy will also be part of the new intramural program.

Gene discovery gives researchers the opportunity to study the function of the gene and its role in cell biology. Such information can provide the starting point for the development of more precise ways to diagnose an illness, and, eventually, a treatment. My own experience in isolating the cystic fibrosis (CF) gene provides a good example of the kind of progress that can be made in understanding a disease once the gene is isolated.

Cystic fibrosis is a common hereditary disease in this country, affecting about 1 in 2000 Americans of European decent. Patients who have CF develop thick mucous secretions in their airways, making them prone to life-threatening respiratory infections. Treatment of cystic fibrosis patients is usually aimed at controlling infections but does not address the molecular root of the problem.

I was part of a team of researchers who isolated the CF gene in 1989. Workers in my laboratory and in Canada had been developing markers and genetic maps that allowed us to zero in on the gene, which is located on chromosome 7. By mapping the gene, isolating it, and determining its DNA sequence, we have begun to understand how the gene causes CF. We learned that the healthy CF gene encodes a protein that regulates salt and water balance inside and outside the cell. The mutated gene, however, encodes a faulty protein that cannot regulate salt and water balance. This malfunction probably accounts for the production of dangerous amounts of thick mucous in the lungs of CF patients.

Once we located the gene, we were able to devise rational ways to treat CF. Information about the role of the gene in cellular processes has allowed us to go straight to the physiologic problem in cystic fibrosis, and to design new, highly specific drugs and gene therapy techniques.

Recently, NIH's Recombinant DNA Advisory Committee approved protocols from five different research groups to use a disabled common cold virus, which normally invades cells in the respiratory tract, to deliver working CF genes to the lung cells of CF patients. The ability to begin such trials less than four years after the gene was discovered is a dramatic example of the power of the new tools of human molecular genetics.

While NCHGR's intramural research program will enhance molecular medicine at the NIH, the extramural program will continue to support research to achieve the goals of the Human Genome Project. In the past year, genome researchers have achieved several significant milestones that put us squarely within reach of our first five-year goals. Dr. David Page and his coworkers at the Massachusetts Institute of Technology, and Dr. Daniel Cohen and his coworkers at France's Centre d'Etude du Polymorphisme Humain (CEPH) independently completed the first continuous physical maps of human chromosomes.

Physical maps are made of cloned pieces of chromosomal DNA that are overlapped by matching up common areas at the ends of the pieces. This results in a contiguous piece, or "contig," that is longer than either of the two original pieces. Continued overlapping of cloned DNA produces a physical map corresponding to large regions of a chromosome. Using this procedure, Dr. Page completed a physical map of the functional portion of the Y, or so-called "male" chromosome, and Dr. Cohen completed a map of the long arm of chromosome 21. Rapid progress is being made by NCHGR-supported investigators to complete physical maps of chromosomes X, 3, 4, 7, 11, 17, and 22.

Physical maps are important to gene discovery because they allow researchers access to small, well-defined, pieces of cloned DNA in which to search for genes. By having the cloned DNA already available, physical maps save months, perhaps even years, and countless dollars in gene hunts. In the past year, physical maps generated by Human Genome Project researchers have assisted in finding the genes for myotonic dystrophy, the major cause of muscular dystrophy in adults; Lowe syndrome; and Norrie syndrome. Already in 1993, Human Genome Project technologies have helped find genes for Menkes syndrome; the X-linked immune disorder agammaglobulinemia; glycerol kinase deficiency; adrenoleukodystrophy, the disorder popularized in the movie *Lorenzo's Oil*; the hereditary cancer alveolar rhabdomyosarcoma; neurofibromatosis type 2; Lou Gehrig's disease; and most recently ended the 10-year search for the Huntington's disease gene.

Improvements in technology have allowed us not only to construct maps of entire chromosomes but also to embark on new strategies for genome mapping. Success in mapping entire chromosomes, in cloning vector technology, in high-quality marker development, and in automation of techniques has led NCHGR to begin two major efforts to construct maps not of single chromosomes one at a time, but rather of the entire genome at once. This large-scale approach promises to be more efficient at generating a crude map that will then need to be refined.

At the genome center located at the Whitehead Institute for Biomedical Research, Dr. Eric Lander will be using a technique known as STS-content mapping to construct a low-resolution physical map of the entire human genome, or approximately 1 STS every 300,000 base pairs. Dr. Lander has previously been testing genome-wide mapping techniques in his work on the mouse genome. The group will identify 10,000 STS markers covering the whole genome. Further

work will be needed to bring the resolution of the physical map to 1 STS every 100,000 base pairs, as called for in the five-year plan for the Human Genome Project.

A second genome-wide mapping project is being undertaken by a group of researchers based at the University of Iowa Cooperative Human Linkage Center. These researchers, in collaboration with scientists in other parts of the country, will be taking advantage of a new type of marker, known as a microsatellite repeat, to refine the genetic linkage map of the entire human genome. These markers are based on DNA sequence and will be particularly useful for gene mapping because they exhibit a high degree of variability in the population, which makes them easy to follow from one generation in a family to the next. In addition, these high-quality markers will be evenly spaced throughout the genome at an average distance of 2-5 million base pairs apart, which will accomplish our five-year goal for genetic linkage mapping. These markers will also serve to connect information from the genetic map to the physical map and eventually to the DNA sequence, thus allowing us to create a unified ultimate map of all the chromosomes.

It is impossible to describe the successes of the Human Genome Project without including the extraordinary international cooperation and substantial participation by other nations. At France's Genethon, Dr. Cohen has not only produced a physical map of chromosome 21, but has also developed methods for making much larger pieces of cloned DNA than were previously possible. Because these clones have lengths of 1 million base pairs or longer, they are called "mega-YACs." Using mega-YACs, Dr. Cohen has begun constructing a physical map of the entire human genome and plans to collaborate with Dr. Lander to ensure that their maps complement each other. Also at Genethon, large numbers of markers for the genetic map are being produced.

In Cambridge, England, Dr. John Sulston has been sequencing the DNA of the roundworm, *C. elegans*, in collaboration with Dr. Robert Waterston at

Washington University in St. Louis. This project has been the most successful sequencing effort to date and has now generated the first 1 million-base pair stretch of sequenced DNA. Britain's Wellcome Trust is creating a sequencing institute for Dr. Sulston to expand his work to human DNA as well as yeast DNA. This center is expected to make major contributions to the world production of DNA sequence. We expect a fruitful collaboration with Dr. Waterston to continue. Obtaining the complete DNA sequence of *C. elegans* will constitute a major milestone in biology and enable scientists to examine the hereditary program that controls the development and function of a multi-celled creature.

I have explained how genome maps help researchers find disease genes and how isolating a gene gives researchers a chance to study at the molecular level the cellular processes that underlie human illnesses. We pursue these efforts because they give us our best hope for treatments for gene-based illnesses. But years may pass between finding a disease gene and developing a widely available treatment. In the meantime, tests derived from gene discoveries will give us the power to provide information to patients about their future health, and sometimes the health of their relatives, in the absence of cures. Along with this power comes a profound responsibility to confront the ethical conundrums that inevitably arise with genetic testing.

Such ethical predicaments are particularly acute when the disease is common--as is the case of cystic fibrosis and breast cancer--and personal physicians find themselves unprepared for the magnitude of the dilemma. I am currently collaborating with Dr. Mary-Claire King, at the University of California, Berkeley, to isolate and identify the gene, called BRCA1, for early-onset breast cancer. A number of other laboratories are also engaged in this search. We are hopeful that the gene will be found sometime this year.

While inheritance of mutations in BRCA1 accounts for only about 5 percent of breast cancer cases, we anticipate that alterations in this same gene

during a woman's lifetime play a role in the vast number of spontaneous breast cancers. Isolation of BRCA1 promises to give us a significant new tool for understanding the molecular basis of all breast cancer.

About 1 in 9 women in the United States will get breast cancer in her lifetime; about 1 in 200 women will get the inherited form. The certain prospect of a diagnostic test for BRCA1 in the near future raises a number of issues--such as public understanding of genetic testing, confidentiality of test results, and test-related stigmatization and discrimination in employment and by health insurers--that will affect large numbers of women and that need to be handily addressed. Fortunately, NCHGR's active Ethical, Legal, and Social Implications Branch already has underway studies of these issues as they relate to cystic fibrosis testing. Since CF and breast cancer are paradigms for common genetic diseases, the results of these studies will shed light on these specific diseases as well as others that will inevitably come. Still, a genetic test for breast cancer, a disease that appears in adulthood, will raise unique questions: at what age should a woman be tested; should children be tested; and, should the test be offered to women who do not have a family history of breast cancer? Many women who because of family history believe they are at high risk for the disease opt for preventive mastectomy. Is this their best option?

These are only a few of the questions an increasing number of physicians must deal with as we enter a new era in molecular medicine and human genetics where tests for susceptibility to common illnesses become available and genetic testing becomes a central part of mainstream medical practice. I cannot overemphasize the seriousness with which we are prepared to address these issues so that disease gene research is used to its greatest benefit.

Mr. Chairman, the budget request for the National Center for Human Genome Research for fiscal year 1994 is $134,549,000. I will be happy to answer your questions.