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THE NATIONAL INSTITUTES OF HEALTH

IMPROVING HEALTH THROUGH MEDICAL RESEARCH

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The National Institutes of Health (NIH) is the world's largest and most distinguished organization devoted to maintaining and improving health through medical research. The NIH is actually a federation of 22 research Institutes and Centers (ICs), each created by Congress and charged with a unique mission. A mission may focus on a given disease, such as cancer, mental illness, or infectious diseases; on a particular organ such as heart, kidney, or eye; or on a stage of development, such as childhood or old age. In other instances, a mission might encompass cross-cutting needs and opportunities, such as the development of research resources or the sequencing of the human genome. The assignment of targeted missions to individual ICs accounts for many of NIH's greatest successes.

Given its size and diversity, "NIH" means different things to different people. Many Americans recognize it as a government agency that supports health research. They associate research advances headlined in the news, as well as new treatments they receive from their own doctors, as products of NIH's work. The more than 20,000 patients who come each year to the NIH's Clinical Center view NIH as an extraordinary hospital where they volunteer to be partners in clinical research and receive experimental treatments for rare diseases. Thousands of students and post-doctoral graduates value NIH and its grantee academic institutions for providing outstanding research training opportunities. And, of course, some 50,000 scientists across the Nation and throughout the world view the agency as an indispensable source of support for critical medical research; eight out of every 10 dollars appropriated to NIH are awarded—through a process of rigorous competition—to investigators in many disciplines who have dedicated themselves to the struggle to improve health and conquer disease. To many of these individuals, NIH connotes the individual IC most closely related to a patient or family member's illness, or a student's interest, or a scientist's area of expertise. Yet, NIH's success is based on its ability to bring to bear the full weight of all of its ICs to solve fundamental scientific questions and address the urgent challenges of disease.

The capability for a truly unified scientific effort can be achieved only through design and perseverance. It requires close interaction among NIH's ICs. These collaborations may be informal, such as scientists discussing their research with one another and lending suggestions, reagents, and equipment to fellow scientists. Or, they may be guided by inter-Institute committees or by NIH-wide coordinating offices such as the Office for Research on Women's Health or the Office of Behavioral and Social Sciences Research. As a "laboratory without walls," the NIH affords unparalleled opportunities to simultaneously address different aspects of a given problem from multiple vantage points. Alzheimer's Disease research, for example, takes place in Institutes devoted to aging, neurology, and mental health, among many others. Advances in cardiovascular disease research are based on insights gleaned from research supported and conducted by many Institutes, including those dedicated to heart disease, stroke, arthritis,

diabetes, and cancer. Similarly, the newly established Center for Inherited Disease Research (CIDR) is co-sponsored by nine participating NIH ICs. The Center is devoted to the genetic analysis of complex, multigenic diseases such as cancers, cardiovascular and pulmonary diseases, hearing and language disorders, neurological diseases, psychiatric disorders, autoimmune diseases, and addictive disorders. These and other complex diseases have been challenging to analyze, since they are often caused by a number of environmental and genetic factors acting in concert. They require very large scale, labor intensive genetic searches.

By maximizing flexibility and encouraging open and collegial dialogue among ICs, as well as between NIH and its sister Public Health Service agencies, research driven by both fundamental scientific questions and pressing public health need can thrive. For example, research supported by the NIH is an essential part of the Administration's comprehensive response to drug abuse and addiction. These problems touch the lives, directly or indirectly, of virtually all Americans. Of special concern is teenage drug use and emerging drug problems, such as methamphetamine use. This research spans the continuum from molecular genetics to drug development and health services research. It continues to provide new insights into the development of medications for the treatment of addiction, to develop new behavioral therapies to meet the unique needs of adolescents, to identify the risk and protective factors for drug use—all in an effort to develop more effective treatment and preventive strategies against this national public health crisis.

The ultimate goal of all NIH research is to improve human health. This research, whether conducted in academic institutions in all 50 States or on the NIH campus, is made possible by a system which fosters both independent thought and collaborative efforts. The success of this approach can be judged from the pages that follow.

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The announcement of an important medical finding on a morning news program appears, at first glance, to be the result of a scientific "eureka!" In most cases, it is not. Medical breakthroughs are usually the result of years of painstaking research that includes episodic disappointments and triumphs, finally culminating in the apparent "breakthrough." The following tells the story of how a major public health problem was virtually eliminated following a 30-year research effort.

Story of Discovery:
The Hib Conjugate Vaccine

In September, 1996 four NIH-supported investigators shared the prestigious Albert Lasker Clinical Medical Research Award for their work in developing vaccines against Haemophilus influenzae type b (Hib). The award called attention to a spectacular accomplishment: that Hib infection, once a major cause of death, deafness and acquired mental retardation in children, is now nearly nonexistent in the U.S.

Almost three decades ago, as many as 20,000 children in the U.S. developed *Haemophilus influenzae* type b (Hib) disease each year. The most common and serious complication of Hib

infection was meningitis, a fatal infection of the membranes covering the brain. Even with effective antibiotic treatment, 5 percent of infants and children with Hib disease died and about 30 percent sustained permanent damage to their central nervous system, in the form of mental retardation, deafness, and seizures. The widespread incidence of Hib infections in the U.S. and world-wide, as well as the serious health consequences of the disease vividly highlighted the need for an effective vaccine, especially in infants and children. This was reinforced by two alarming observations—that children in crowded day-care centers were experiencing a 10-fold higher incidence of Hib meningitis than the general population, and that Hib developed resistance to commonly used antibiotics.

Two teams of researchers began working on parallel, but separate, paths to develop a vaccine, choosing to use the Hib bacteria's outer coat of polysaccharide (sugar) as the immunity-stimulating component of the vaccine. Many of their colleagues believed it would be nearly impossible to develop a vaccine for infants using a polysaccharide. Nevertheless, by the early 1970's the scientists had prepared Hib polysaccharide that was suitable for clinical trials. The polysaccharide vaccine proved safe and effective in children older than 18 months of age. Many more years of work supported by NIH and pharmaceutical companies would lead to the eventual licensing and marketing of three Hib polysaccharide vaccines for children older than 18 months.

Although Hib infections occurred mostly in children up to age 5, infants six to twelve months old were especially vulnerable. Unfortunately, Hib polysaccharide vaccine failed to stimulate immunity in these infants, the age group with the highest incidence of serious disease. The scientists set out to make a vaccine that would also be effective in infants, drawing from research carried out in the 1920's and 30's which showed that polysaccharides elicit a stronger immune response if they are chemically attached to a protein. Between 1980 and 1983, both groups succeeded in attaching the Hib polysaccharide to a protein, although they used different proteins and different methods for attaching the polysaccharide to the protein. These were the first "conjugate" vaccines to ever be developed. Both Hib conjugate vaccines elicited higher levels of immunity in adults and children than did the polysaccharide alone. Most importantly, however, these conjugates also elicited an immune response in infants. Extensive clinical trials confirmed that Hib conjugates prevented meningitis in infants, and the Hib conjugate vaccines were licensed by the FDA in the mid-to-late 1980's.

Today, Hib conjugate vaccines are part of the routine pediatric immunization series given to babies starting at the age of 2 months. As a result, Hib meningitis and the other systemic infections caused by Hib—such as epiglottitis, osteomyelitis, and septic arthritis—have virtually disappeared in the U.S., Canada, Iceland, Finland, Sweden, Norway, Germany, Switzerland, and Holland. These studies have pointed out that it is theoretically possible to eradicate both Hib organisms and disease, similar as the case with smallpox and what appears to be occurring with poliovirus and poliomyelitis.

Impressive as this story of discovery is to date, its legacy promises to be even greater. The conjugate concept developed by these researchers is making possible the development of vaccines

against other bacteria with polysaccharide coats. Scientists are already working, for example, on conjugate vaccines to prevent pertussis, typhoid fever, dysentery, pneumonia, otitis media, and illness from *E. coli* 0157 contamination of beef. The Hib story exemplifies the power of scientific partnerships, for although the teams of researchers worked independently, they routinely and consistently shared their knowledge and insights with one another, ensuring an effective solution to a serious public health problem.

Researchers in non-medical industries also often make innovative use of the findings from NIH's medical research. This can lead to the development of commercially important products, such as the ones described below.

Story of Discovery: Beyond the Boundaries of Medicine

An examination of the "scientific pedigrees" of many non-medical biotechnology products now in the marketplace reveals a vital dependence on the knowledge of basic life processes and the laboratory tools that have emerged from decades of NIH investment in fundamental research. Furthermore, it is apparent that the private sector is closely monitoring advances in medical science and is acting quickly to incorporate new knowledge and methods into valuable commercial applications. The scientific history of several commercially important non-medical biotechnology products illustrates this point.

Genetically engineered crop plants are currently a prime area of innovation and new product development in the biotechnology industry. Nearly 20 such "transgenic" plants are commercially available, and several dozen more are poised to hit the marketplace in the next several years. The first plant to be genetically engineered for quality improvement was developed by Calgene, a U.S. biotechnology company that, in 1994, introduced the *Flavr-Savr™ tomato* to the fresh produce market. The Flavr-Savr™ has been genetically engineered to delay the substantial softening of tomato flesh that normally accompanies ripening. This modification was achieved by inserting an "antisense" gene into tomato DNA that prevents the production of a protein needed for softening the tomato flesh. The NIH was a principal supporter of much of the research underlying antisense technology, including basic recombinant DNA research in the 1960s and 1970s and research in the first half of the 1980s, in which scientists demonstrated that antisense methods could be used for gene regulation in a wide variety of cell types. Agricultural scientists successfully adapted the technique to the Flavr-Savr™ tomato just a few years later.

In 1996, two U.S. agricultural companies, Ciba Seeds and Mycogen Seeds, began to market *hybrid corn plants that are resistant to the European Corn Borer*, a notably destructive insect which has long plagued U.S. farmers. The pest resistance feature of the seeds was the result of genetic engineering. Corn DNA was modified to include a "foreign" gene—from a common soil bacterium—for the production of insecticidal crystal proteins that kill the European Corn Borer. Although corn capable of producing these crystals emerged from agricultural research in the early 1990s, the knowledge necessary for its development emerged out of earlier medical research. NIH-funded researchers, for example, were the first to isolate a crystal protein gene in 1981. This

accomplishment opened the door to an expanded research effort to identify the genes and molecular pathways involved in crystal protein production. The development of genetically engineered corn also depended on novel methods for transferring foreign genes into corn plants—technology which emerged from NIH-funded medical research in the late 1980s.

A third illustrative case is the growing commercial application of laboratory *DNA typing* as a basis for distinguishing differences between organisms, including humans, animals and plants. DNA typing relies heavily upon a technique known as RFLP analysis. RFLP analysis has subsequently been applied successfully to crime scene analysis, paternity determination, farm animal husbandry, quality control of microorganisms used in industry, and ecological and environmental studies. The development of the RFLP analysis technique was predicated on a number of pivotal medical science advances, many of which were supported by NIH in the 1970s, including understanding the role of restriction enzymes, DNA hybridization methods, and laboratory tools for separating DNA fragments.

Areas of Research Emphasis

These stories of discovery illustrate the difficulty of predicting all the applications of medical research. It is still important, however, to establish research priorities. Each year, the NIH Director identifies Areas of Emphasis which show the most promise for addressing public health needs and yielding medical advances that will lead to improvements in human health. Accordingly, six Areas of Research Emphasis have been identified for FY 1998. Five of these were also used in the development of the FY 1997 budget—The Biology of Brain Disorders, New Approaches to Pathogenesis, New Preventive Strategies Against Disease, Genetic Medicine, and Instrumentation and Computers. A new area of emphasis, "New Avenues for Development of Therapeutics" emerged from consideration of Institutes' and Centers' (ICs) proposals for new initiatives. For FY 1998, a number of enticing opportunities have emerged in each of the Areas of Emphasis. These include: new efforts in developmental neuroscience to explore how different types of nerve cells form and organize themselves in the developing brain; the design of diagnostic tests and strategies to respond to emerging food- and water-borne infections as well as the looming threat of cross-species infections; additional efforts to decipher the genome using gene "knockout" techniques; innovative technologies for visualizing and analyzing complex interactions among the molecular building blocks of life—DNA, RNA, proteins, and other substances; and new efforts to assess a broad range of medications for pediatric diseases and conditions.

This approach of providing incentive funding for a focused initiative has successfully stimulated research and fostered collaborations among ICs. For example, within the Biology of Brain Disorders area, an initiative, spurred by the President's strong commitment to spinal cord research, was begun last year to encourage research on spinal cord injury. Spinal cord injury is experienced by approximately 10,000 Americans—more than two-thirds of them under age 30—with often devastating impact. The initiative was kicked off with a major workshop that convened experts on spinal cord injury along with leaders from other scientific areas to foster new ideas and collaborations. As a result of the workshop, a program announcement was issued

highlighting important relevant research topics, including the mechanisms of secondary injury that damage spinal cord cells in the hours immediately after trauma; immune responses that may help or hinder recovery; the identification and study of survival and growth factors; systems that guide growing axons to find appropriate destinations and make functional connections; the development of improved animal models for research on therapeutic interventions; and systematic studies of rehabilitation. NIH expects to continue this strong commitment to spinal cord injury research.

Major medical breakthroughs are usually the result of years of research involving many investigators and laboratories. In the space of a single year, however, NIH-supported research yields many "incremental" advances, seemingly smaller but equally significant findings that represent chapters in an ongoing story of discovery. Each advance has a rich history of science behind it, and it is hoped, a future of clinical application ahead of it.

Advances in the Biology of Brain Disorders

A Window into the Neurobiology of Drug Craving. The imaging technology known as Positron Emission Tomography (PET) has allowed researchers their first glimpse of the brain changes triggered by drug craving. PET scans were taken while human volunteers who abuse cocaine were exposed to environmental "cues" associated with drug use, such as drug paraphernalia. The visual images that were obtained revealed that brain regions involved in several forms of memory (working, episodic and emotional) were specifically activated when the addicts reported craving. In contrast, the same cocaine-related cues did not elicit craving in normal volunteers, and neutral cues (e.g., arts and crafts items) failed to elicit craving in either group of volunteers. This study provides the first evidence that drug craving may be mediated by brain systems involved in memory. It also suggests the relevance of memory processing to future studies of craving in drug addiction and to the development of therapeutic interventions. Such findings likely will contribute to understanding other appetitive disorders that involve powerful urges.

Understanding Nerve Cell Connections. Nerve cells communicate with one another and with other body cells via specialized points of contact known as synapses. Investigators are studying the synapse, between a nerve cell and muscle cell, to find clues to how synapses form and operate. Scientists knew from previous studies that the proteins agrin and MuSK (muscle specific protein kinase) play a role in synapse formation at the synapse between the nerve and the. muscle, the so-called neuromuscular junction. To better define the function of these two proteins, researchers created mice in whom the gene for either agrin or MuSK was "knocked out" (inactivated). The mice missing either protein had severely defective neuromuscular synapses, which left them unable to move or breathe. This suggests that agrin and MuSK are both required for motor nerves to form synapses with muscle. These and other studies are beginning to reveal how a two-way chemical conversation between the nerve and muscle cell guides the formation of the neuromuscular synapse. This knowledge is also an important step toward understanding nerve cell communication and synapse formation in the brain and could also lead to a better understanding of neuromuscular disorders such as the muscular dystrophies.

Learning About Learning. Investigators have begun to identify specific changes that take place in the brain when adults learn a new skill. Researchers used the imaging technique known as functional magnetic resonance imaging (fMRI) to examine changes in brain blood flow that occurred as volunteers were learning a simple motor skill—a particular sequence of finger-to-thumb tapping. As the volunteers became more adept at the finger tapping exercise through practice, the fMRI imaging revealed increased activity in the primary motor cortex region of the brain. This study provides an elegant view of the neural mechanisms involved in learning and memory and suggests that learning and remembering a motor skill occurs through a slowly evolving reorganization and enlargement of the brain "circuits" that are involved in a particular task.

New Approaches to Pathogenesis

Understanding How Cigarette Smoking Causes Lung Cancer. Although it has long been known that smoking is the single most important risk factor for lung cancer, it was unclear just how cigarette smoking causes cancer. Scientists recently discovered how a chemical in cigarette smoke, benzo[a]pyrene, damages a gene, *p53*, that normally suppresses the uncontrolled growth of tumor cells. In the body, benzo[a]pyrene is converted into a potent cancer-causing agent known as BPDE. BPDE in turn preferentially attaches to, or binds at three particular spots on the *p53* gene—sites which are documented "hotspots" for the genetic alterations commonly found in many patients with lung cancer. If the body is unable to repair the damage to the *p53* gene caused by BPDE, the resulting inability to suppress uncontrolled cell growth may lead to cancer. In revealing BPDE's role in the transformation of normal human lung cells into cancerous cells, this study shows, at the molecular level, how exposure to the carcinogen in cigarette smoke leads to lung cancer.

The Ongoing Story of Obesity. Obesity has become epidemic in our Nation—one third of all U.S. adults are considered obese, and obesity is on the rise in children as well. Obese individuals are at increased risk for numerous debilitating and costly chronic diseases, such as diabetes mellitus, cardiovascular disease, hypertension, gallbladder disease, and certain cancers. Recently, scientists have been making rapid strides in understanding obesity at the molecular level—witnessed by important new discoveries regarding the *obese (ob)* gene, its protein product (leptin), and the cellular receptors for leptin.

Investigators have also found important clues to how obesity is a risk factor for diabetes. In one study, scientists demonstrated that two genetic mutations which cause diabetes in animals—the *diabetes (db)* mutation in the mouse and the *fatty (fa)* mutation in the rat—are actually mutations of the gene for the leptin receptor. In another study, researchers added high levels of leptin, comparable to those present in many obese individuals, to cultured liver cells that contained the leptin receptor on their cell surface. The high leptin levels caused marked changes in a number of complex insulin-induced activities in the liver cells. This result implies that, in obese individuals, leptin may act directly on liver cells to modulate glucose metabolism and that leptin may play a role in the onset of non-insulin dependent diabetes mellitus.

Researchers studying metabolism have developed a strain of apparently healthy mice that, although they eat more food—including more high-fat food—than do normal mice, stay about 10 percent leaner. The secret? The researchers had "knocked out" a gene called RII-beta. This gene enables normal mice to produce a component of the PKA (for cyclic AMP-dependent protein kinase A) protein, which plays an important role in regulating cellular metabolism. In the absence of the RII-beta gene, the animals' brown fat was stimulated to burn off the extra calories consumed, instead of turning them into the more familiar white fat. "Brown" fat is fatty tissue the body can burn to produce heat. Because brown fat is found almost exclusively in infants, it is unclear how directly applicable this finding will be to obesity in children and adults. These knockout mice, however, will provide an important model system for studying the molecular basis of obesity and, ultimately, may lead to effective treatments for this major public health problem.

Understanding How HIV Infects Cells. Scientists have known for some time that immune system cells with a surface protein receptor known as CD4 were the preferred targets of HIV. They also realized that CD4 alone was not sufficient to allow HIV to fuse with immune cells and infect them. At least one, and possibly more, surface molecules had to be involved, but their identity eluded researchers for a decade.

Now, NIH-supported scientists and others have discovered two proteins on the surface of target cells that act as "cofactors" or coreceptors with CD4, allowing HIV to fuse with the immune cell and infect it. The first cofactor protein to be identified is called CXCR4. In conjunction with CD4, it allows infection by the strains of HIV that are found in patients in the later stages of HIV disease, when their immune system is compromised. The second protein, named CKR5, acts as a fusion cofactor for the strains of HIV most commonly found in individuals during the early, symptom-free stage of infection. These two proteins are potential targets for the development of anti-HIV drugs that block or interfere with the binding of HIV to the receptors. These findings could also provide clues for developing a vaccine that might work, for example, by triggering the body to produce antibodies against the receptors, thus conferring resistance to HIV.

This work also sheds light on a previously puzzling observation that a small subset of the population is seemingly immune to HIV, despite repeated exposure. Scientists recently determined that just over one percent of Caucasians inherit two mutated, nonfunctional copies of the gene for the CKR5 protein. These individuals are, for all practical purposes, genetically resistant to HIV infection, even when heavily exposed. In this case, inheriting a genetic "defect" is a life saver—HIV is consequently unable to gain entry into the immune system cells because the cell surface lacks the fusion cofactor. About 20 percent of Caucasians have inherited one mutated, nonfunctional version of the CKR5 gene and one normal copy. Although these individuals are susceptible to infection with HIV, they progress to AIDS more slowly than do infected individuals with two normal CKR5 genes. These mutations are not observed outside the Caucasian population.

Although its role as a fusion cofactor for HIV is a recent discovery, CKR5 was previously known to be a cell surface protein, called a chemokine receptor, that functions in cell-to-cell communication in inflamed joints. At first glance, these two roles of CKR5 are seemingly unrelated. The nature of that connection is beginning to unfold, however, from studies of immune system cells and the molecules they secrete. Immune cells known as CD8+ T cells secrete a type of signaling molecule known as beta chemokines, which normally function by recruiting inflammatory cells to the site of an infection. Scientists have discovered that beta chemokines are multi-talented—they also suppress HIV replication in both the blood and the lymph nodes taken from HIV-infected people. Researchers also recently discovered that three specific beta chemokines suppress HIV replication by occupying (blocking) CKR5, thereby preventing HIV from entering its target cells.

Researchers are also gaining new insights into how the body controls HIV replication. It has been known that some immune cells involved in inflammatory responses secrete chemical messengers called cytokines, and that some naturally occurring cytokines boost HIV replication in cultured cells, while others are suppressive. These studies suggest that HIV replication may be regulated by a delicate balance among the body's own cytokines. By altering this balance, HIV replication can be dramatically influenced in the test tube, and potentially even in the body. A complete understanding of the interactions between immune system molecules and HIV could potentially lead to the development of therapeutic strategies capable of regulating this balance in favor of immunosuppression.

New Preventive Strategies Against Disease

New Findings About Optimal Time and Conditions for Conception. Investigators have discovered that, in healthy women, the highest probability of pregnancy each month occurs during the six day window ending on the day of ovulation. This finding challenges the long-accepted medical belief that women are most fertile a few days before and after ovulation. Other researchers determined that the simple practice of douching can significantly reduce a woman's monthly chance of conception. Compared to women who did not douche, women 18-24 years old who douched were 50 percent less likely to conceive. Older women who douched experienced reduced fertility as well, but to a lesser degree (30 percent reduction for women 25-29 years old and 6 percent reduction for women 30-39 years old). These studies provide critical information for couples trying to achieve or avoid pregnancy.

New Hepatitis Virus Discovered. A collaboration between government and industry scientists has resulted in the identification of a new infectious agent, the hepatitis G virus (HGV). The virus is very common—it was detected in up to 2 percent of the volunteer blood donor population and its presence in the general population is likely to be 2-4 fold higher. Although it has not been firmly established whether HGV infection results in disease, the virus frequently persists in the body for many years and is transmissible through blood transfusions and other blood-borne routes. Determining the disease-causing ability of HGV is critical. If the virus proves to have serious disease implications, it will be urgent to develop a screening assay to

ensure the safety of the Nation's donor blood supply. A preliminary study of HGV infection among prospectively followed transfusion recipients and their donors suggests, however, that HGV may account for only a small proportion, if any, of the transfusion-transmitted cases of hepatitis not caused by the known types of hepatitis viruses. While this finding is welcome news for those infected with HGV, it also suggests that another, as yet unidentified, agent—conceivably more prevalent and more clinically significant than HGV—contributes to transfusion-associated hepatitis. This possibility highlights the vital importance of accelerating viral discovery programs.

Advances in Genetic Medicine

International Team Completes DNA Sequence of Yeast. A worldwide collaboration involving nearly 100 laboratories and some 600 researchers, many supported by the NIH, has culminated in the complete sequencing of the genome of *Saccharomyces cerevisiae*, or brewer's yeast. Containing 6,000 genes, the yeast sequence is the largest genome to be completely deciphered to date. The yeast genome is of particular interest to medical scientists because about one-third of yeast genes are related to those in the human. These similarities suggest that the shared genes play a critical role in cell function in both species, including the essential processes of DNA replication, repair of damaged DNA, protein synthesis and transport, and control of metabolic processes. In cancer research, yeast has emerged as an important model for studying the control of cell division. Despite the great deal already known about yeast, researchers know the function of only about half of its 6,000 genes. The additional research required to understand the role of the remaining genes eventually will provide the first look at how a living cell functions as a unit.

On-Line Maps of the Human and Mouse Genomes. A team of over 100 scientists from government, university, and commercial laboratories around the world have developed a map that, so far, pinpoints the locations of 16,354 genes in human DNA—approximately one-fifth of the entire complement of human genes. NIH recently posted the map on the World Wide Web (http://www.ncbi.nlm.nih.gov/science96/). The map contains extensive links to supporting data about the DNA and protein sequences associated with the mapped genes and offers links, as well, to references in the medical and research literature. Painstaking effort has been taken to present the latest research information about genes and their function in both health and disease in a well organized and easily understandable manner. Thus, the Web site provides scientists and medical personnel, as well as students and the public with a user friendly and continuously updated window of progress on one of the most extraordinary scientific undertakings of the 20th century—the mapping of the human genome. Although it is only partially complete, the mapping project already has advanced our understanding of the genetic basis of many diseases by significantly accelerating a number of disease gene hunts. The map was instrumental, for example, in locating and isolating genes responsible for Alzheimer's disease, inherited colon cancer, achondroplasia (a bone growth disorder resulting in short stature), a type of endocrine tumor, and a congenital digestive disorder known as Hirshsprung's disease.

Another team of researchers recently completed a five year project of mapping the mouse genome. Available on-line as well, the mouse map can also be accessed, by electronic link, from

the human gene map. Because the mouse and human genomes share many similar genes, and capabilities to genetically manipulate the mouse genome (e.g., by adding or deleting specific genes associated with identified traits) are evolving so rapidly, the mouse genome map affords intriguing and informative insights into the function of many human genes.

Advances in Instrumentation and Computers

"Visible Humans" Change the Teaching and Practice of Medicine. The world's first "computerized cadavers," known as the Visible Human Male and Female, are revolutionizing the teaching of anatomy and the practice of medicine throughout the world. The implementation phase of the project began three years ago when a 59-year old female heart-attack victim and a 39-year old male executed for murder donated their bodies to science. They became the world's first digitized humans when NIH scientists obtained detailed CT (computed tomography) and MR (magnetic resonance) images of their bodies, and then cut the bodies into extremely thin crosswise slices that were photographed at high resolution. The images were compiled into a computer database, providing complete, anatomically detailed, three-dimensional representations of the human body. More than 500 licensed users have developed remarkable applications for the data, as well as technologies to create Visible Human-like representations of live patients. Examples of these innovations include non-invasive colon cancer screening; simplified plastic surgery; patient-specific rehearsal of prostate cancer surgery; surgical and spinal tap simulations; the Recyclable Cadaver, which allows for repeated, "reversible" dissection; radiation absorption modeling; and crash testing.

New Avenues for Development of Therapeutics

A Step Closer to Replacing Daily Injections with Pills. NIH-supported researchers, collaborating with industry partners, recently achieved a breakthrough that could make it possible to replace the costly and painful injections currently used for treating conditions such as anemia, diabetes, and human growth hormone deficiencies with an easily swallowed pill. Erythropoietin (EPO) is a naturally occurring substance, produced by the kidney, that stimulates the body to produce red blood cells. Genetically engineered EPO is presently used to treat anemia caused by kidney failure, cancer chemotherapy, and AZT treatment for HIV infection. Currently, EPO must be injected because large, natural proteins such as EPO are destroyed in the stomach if taken orally. Recently, scientists developed a very small molecule that mimics the action of the much larger EPO protein. The new molecule may serve as a model for designing a nonprotein drug capable of stimulating red blood cell production and yet small enough to be administered in pill form. In addition to its potential for improving quality of life, the development of a new generation of oral drugs has significant economic implications. For example, EPO is today the single largest revenue producer of the biotechnology industry.

Mounting an Effective Immune Response Against Tumor Cells. Although tumor cells produce a variety of molecules that are recognized by the body's immune system, the tumor molecules elicit only a mild immune response, one that is not vigorous enough to completely

destroy the tumor. This immunological timidity has challenged researchers to devise methods for "presenting" tumor molecules to a patient's immune system in a way that will evoke a strong immune response. Researchers recently made a promising breakthrough using a mouse model to study the immune response to tumors. It was known that the antitumor response involves a complex balance between signals that stimulate or inhibit the immune system, and that an immune cell protein known as CTLA-4 is one of the inhibitors. Building upon these findings, the researchers used antibodies to block the production of CTLA-4 in mouse immune cells. Most of the mice treated with these antibodies rejected their tumors; in sharp contrast, every one of the untreated tumor-bearing mice died. The work establishes important principles of immunology and suggests an innovative strategy for cancer immunotherapy.

Clinical Advances in Treating and Assessing HIV Disease. A NIH-supported clinical trial involving HIV-infected patients has demonstrated that infusions of a protein called interleukin-2 (IL-2) lead to substantial and sustained increases in the number of CD4+ T cells in the patients. These cells, which play a critical role in the human immune system, are the preferred target of HIV. In the trial, patients who received a genetically engineered version of IL-2 every two months in five day cycles, along with anti-HIV drug therapy, experienced an average two-fold increase in CD4+ T cell counts compared to patients who received anti-HIV drug therapy alone. IL-2 is the first experimental therapy to bring about significant long-term increases in CD4+ T cells without unmanageable side effects. A follow-up trial is planned to determine whether CD4+ T cell increases will also translate into improved health and prolonged life for HIV-infected patients.

A recent study showed conclusively that anti-HIV drugs can prevent AIDS-defining illnesses and reduce the risk of death in asymptomatic people with intermediate-stage HIV disease. The study compared the clinical benefits of four different anti-HIV treatment regimens: AZT alone, AZT plus ddI, AZT plus ddC, and ddI alone. These anti-HIV drugs work by inhibiting the activity of an enzyme necessary for HIV replication. The trial results demonstrated that the two combination regimens and the ddI alone regimen were superior to AZT alone in preventing at least one of the following serious consequences of HIV-infection: a significant decrease in the number of CD4+ T cells, the appearance of an AIDS defining condition, or death. Variations in the clinical benefit of a particular regimen were shown to be a function of previous AZT use; patients who had never taken AZT benefited most from the combination of ddC plus AZT, while those previously on AZT benefited most from either ddI alone or ddI plus AZT. This information about the relationship between treatment history and the effectiveness of specific anti-HIV drug regimens will be useful to health care providers in designing individualized treatment strategies for their patients.

There is new evidence that an individual's risk of disease progression can be predicted from the level of HIV genetic material (RNA) detected in the bloodstream. Researchers measured the HIV RNA levels of 180 HIV-infected patients twice yearly for ten years, while also monitoring their health status. Higher levels of HIV RNA were associated with faster progression to AIDS or death. The study also showed that a patient's prognosis—as predicted by HIV RNA

measures—was independent of their level of CD4+ T cells. These results suggest that HIV RNA level is a more consistent and accurate predictor of disease progression than is CD4+ T cell count. Improved methods of predicting disease progression in HIV-infected individuals will enable health care providers to determine the most appropriate treatment strategies for HIV infected people, and will provide an important tool for assessing the effectiveness of new and potential anti-HIV therapies.

These advances are only a few examples of the many exciting discoveries coming from NIH research. It is, however, impossible in the space of a few pages to fully convey all of the research steps necessary for the development of new treatments, diagnostic methods, and prevention strategies. One of the intermediate steps in the process—gene discovery—has received considerable attention in the media. The announcement of the discovery of a new gene often generates tremendous expectations that a new treatment or cure is just around the corner. It is important to understand, however, that there are many critical intermediary steps between identification of a disease gene and new medical treatments.

Discovery of Human Disease Genes

The isolation of a gene is an important milestone on the path to understanding the role that genetic material plays in who we are, how we function, and what causes some disorders. This past year has witnessed the isolation of genes responsible for or associated with many important human diseases and conditions, including:

- Progressive Myoclonus Epilepsy 1, a rare inherited form of epilepsy
- Retinitis Pigmentosa, a progressive loss of vision
- Inherited basal cell carcinoma, a form of skin cancer
- Werner's Syndrome, which causes premature aging
- Over 50 syndromes involving head and face abnormalities associated with birth defects
- Hereditary hemochromatosis, an iron metabolism disorder causing multiple organ failure
- Hereditary pancreatitis, which often leads to cancer of the pancreas
- Polycystic kidney disease
- Myelodysplastic syndrome, a bone marrow disease
- Susceptibility to nerve gases and pesticides
- An inherited form of Long QT syndrome, an irregular heartbeat which can lead to sudden death
- Severity of Attention Deficit Hyperactivity Disorder
- Alport's syndrome, which involves deafness and kidney disease

In 1996, NIH-supported researchers made important progress towards identifying additional disease genes. They were able to determine the chromosomal locations of genes involved in many important human diseases, including:

- An inherited form of Parkinson's Disease

- A hereditary predisposition to prostate cancer
- Cystinuria, a metabolic defect which causes kidney stones
- Nephrotic syndrome, a congenital kidney disease
- Many forms of hearing loss, as well as genes responsible for normal hearing development and/or function

Identifying the chromosomal location of a gene is an important accomplishment because knowing the location of a gene narrows the "haystack" (chromosomes) that must be searched in the quest of the "needle" (gene).

Another important step in medical research is the development of a model system for studying the origins and consequences of human disease and disability. Animal models of human disease have proven to be essential tools for progress in understanding many diseases.

Animal Models of Human Disease

Human beings are very complex biological organisms, but our cells contain the same fundamental components as those of all living things. Researchers can, therefore, learn much about the way human cells and genes work by studying simpler organisms. Mice are particularly valuable research animals for many reasons. They share many physiological and genetic similarities with humans, they are easily maintained in the laboratory, they reproduce rapidly, and their genetics have been thoroughly studied. Because of this, the role of genes can be determined relatively quickly in mice and other animals and these findings can often be applied to understanding human genetics.

Researchers who want to use an animal model to study a human disease first look for animals that are particularly prone to developing certain tumors, metabolic disorders, or the disease of interest. Many mutant strains of mice have been specially bred for such research. These mouse models can then be used for studying the physiological course of a disease, determining the identity and function of the genes and proteins involved in a disease, testing new treatments, and developing and testing methods for preventing disease.

In many instances, there is no comparable animal model of a disease; however, researchers are able to develop them by modifying the genetic make-up of test animals. This strategy has yielded valuable, and sometimes unexpected, information about the role of a specific gene in healthy and disease states, as well as knowledge about the complex cellular mechanisms that regulate the gene. There are different methods for creating an animal model of a human disease. One technique, the production of so-called "transgenic" animals, involves the insertion of a "foreign" gene (normal or altered) into an animal embryo. Researchers can observe the effect(s) of the new gene in the animal, gaining insights into its role in development or in a physiological process. In another approach, known as "knockout" experiments, scientists inactivate a particular gene, and then observe what effects, if any, this has on the mouse. In this way, it is sometimes possible to infer the function of a gene by noting the problems that arise in its absence. Adding a "foreign" gene to a mouse or "knocking out" a normal mouse gene may recreate a condition in the mouse

similar to a human disease. Researchers may then learn something about the role of that gene and also have an animal model for testing new treatments.

This year, researchers have succeeded in developing a number of new animal models that will provide new knowledge about human disease and facilitate assessments of new treatments and preventive regimens. Examples include:

- A mouse model of Alzheimer's disease that, for the first time, exhibits both the behavioral and neuropathological symptoms of Alzheimer's disease
- A rat model of autism
- Strains of mice that are predisposed to drug-mediated euphoria, which have already allowed researchers to localize two genes that influence alcohol consumption
- Animal models for 5 different rare inherited metabolic conditions: tyrosinemia type 1 (mouse), adenine phosphoribosyltransferase-deficiency (mouse), Fabry Disease (mouse), Krabbe disease (dog) and glycogen storage disease, type VII

In the past year, NIH-supported researchers have also used animal models and knockout experiments to gain critical insights into how genes function in human health and disease. Below are just a few examples of the gene discoveries made in animal models that are providing tantalizing clues to understanding human disease:

- AML1, a gene linked to acute myeloid leukemia, which appears to be a master regulator of blood cell development
- A cell-growth control gene, p27, which is necessary for a normal pituitary gland and normal body size
- The E2F-1 gene may be a new "tumor suppressor" gene, whose absence leads to tumors in many tissues
- A regulatory gene, Brn3.1, may play a role in inner ear defects and deafness
- A gene for a component of protein kinase A, which plays a role in metabolism and energy processing
- A gene for a surfactant protein, which functions in protecting the lungs against infection
- The genes for the agrin and muscle specific protein kinase (MuSK) proteins, which have an essential role in forming nerve connections to muscles during development
- The ATM gene, which is important for repairing damaged DNA; its absence results in a severe syndrome of neurological impairment and cancer predisposition called ataxia telangiectasia
- One of the serotonin receptor genes, which appear to increase alcohol consumption
- Multiple genes that appear to be involved in drug craving and addiction

With the progress in developing animal models and in discovering and isolating genes come new challenges to ensure that this information is used appropriately. The potential for inappropriate uses of new knowledge about the genetic basis of disease poses additional challenges such as ensuring responsible medical practices with respect to genetic testing and protecting the confidentiality of medical and research information.

Future Challenges: Advances in Genetics—Responsible Medical Practices and Privacy Issues

Information based on molecular genetics is becoming increasingly more important in medical practice and in

the setting of public health policy. In recent years, researchers have identified genes and proteins that play a key role in many diseases, including cancer, as well as in complex human disorders such as hypertension. In addition, rapid progress in the mapping and sequencing of the human genome is facilitating the identification and isolation of additional human disease genes. As knowledge increases regarding the genetic basis of disease, so too does the potential for inappropriate uses of genetic information, such as discrimination and stigmatization. Genetic testing can move rapidly from the research setting into clinical practice, but not necessarily with appropriate technical oversight or requirements for evidence of health benefits. For example, misunderstandings concerning the predictive ability of such tests, and any shortcomings they may have, can have serious implications regarding the very personal decisions that must be made once the results of the tests are known. Society must also find rigorous means of ensuring the confidentiality of all medical and research information and materials. The widespread use of such genetic information can have far-reaching consequences related to the ability to obtain life and health insurance as well as considerations of hiring practices for employees. Efforts are needed to stimulate an informed, broad-based national dialogue about how to monitor data access without hampering treatment or research and, at the same time, to ensure individual privacy while enhancing the quality of health care.

Ensuring steady progress in improving health and quality of life will necessitate a strong infrastructure in which to conduct research. Widespread changes in the financing and delivery of health care are threatening the stability of academic health centers. Investigators at these centers, which are located in every state, conduct much of the medical research funded by NIH. One of the many challenges facing NIH and the nation is maintaining that research infrastructure, including the academic health centers as well as the NIH Clinical Center.

Future Challenges: Updating the Clinical Research Center

Basic science and clinical medicine converge, each amplifying the other, within the walls of the NIH Clinical Center. Currently, an average of 20,000 children and adults are referred annually to the Clinical Center for experimental treatment and study. These patients account for approximately 65,000 inpatient days and 70,000 outpatient visits for frequently occurring, as well as rare or "orphan," diseases.

The Clinical Center is, on several counts, an indispensable national resource. First, from the perspective of medical science, the Center benefits from an unparalleled breadth and depth of expertise; researchers and NIH administrators bring the resources of the surrounding NIH campus to bear on the medical challenges encountered within the Center's walls. Second, the Clinical Center remains one of the premier research training sites in the world. Building on its distinguished record in research "mentoring," the Clinical Center recently launched a formal clinical research training initiative.

The FY97 budget requested $310 million to fully fund the cost of constructing a new state-of-the-art Clinical Research Center. Congress approved the new Clinical Research Center project with

an initial appropriation of $90 million. An international competition yielded a design concept that melds both the form and the function of the existing Clinical Center. Detailed design work now is underway to relocate the existing Clinical Center entrance and modify the site to facilitate construction of the new Clinical Research Center. The project development team, consisting of a development manager, architects, engineers, construction manager, and specialty consultants, is in place. Development of detailed program requirements is substantially complete, and NIH expects that the total cost of the facility will equal $310 million, which is why the Budget requests a total of $220 million in appropriations and advanced appropriations, in addition to the $90 million Congress appropriated in FY97. Construction completion and occupancy of the NIH Clinical Research Center are scheduled for 2002.

Finally, as the Nation looks toward the future, the aging of the baby boomers portends a significant burden to the national healthcare system. The effectiveness of this system and the quality of treatment delivered is dependent, in part, upon continuing medical innovation, which is the result of NIH-supported research.

Future Challenges: The Aging Population—Healthcare, Economics and Medical Research

The next three decades will witness a revolution in America's demographic profile. The most profound change will be a doubling in the number of Americans age 65-and-over, from 33 million today to more than 69 million. A substantial portion of this increase will come from a tripling in the number of persons age 85-and-older, from 3 million to 9 million. Nearly half of those in the latter group will suffer from Alzheimer's disease or other dementias. As a group, they also will be more economically disadvantaged, more fragile physically and emotionally, more likely to live alone, and use health services far more than individuals age 65-84.

Maintaining the health of our elderly citizens and ensuring the quality of and access to health care services under these circumstances presents the Nation with an unprecedented challenge. Remarkable scientific strides in recent years have been paralleled by public health efforts, which, based on research information, are encouraging greater responsibility for healthy behaviors across the lifespan. Preventive strategies and effective treatments for chronic debilitating diseases have improved overall health and quality of life for the elderly, extending the duration of productive adult life and pushing back both the boundaries and the meaning of old age. In general, the future aged are expected to be healthier and more active than their counterparts today, in part because of HHS-supported studies of aging and its common diseases.

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The NIH plays a vital role in the Nation's medical research enterprise. NIH-supported research generates knowledge that leads to improvements in the health and quality of life of the American public. It also provides a continually expanding knowledge base for the development of commercial products by the pharmaceutical and biotechnology industries and other key

components of the national medical research infrastructure. Through its support of research training in intramural and extramural settings, moreover, the NIH continues to produce highly trained scientists who rise to leadership positions in publicly funded research and in the biotechnology and related industries.

As life expectancy increases, the number of people suffering from chronic diseases will sky-rocket, placing ever greater demands on entitlement programs. Noncommunicable chronic diseases and other age-related conditions, such as heart disease, cancer, neurological and emotional disorders, stroke, and injuries, will become the leading causes of death and disability and will strain the Nation's capacity to provide social support and healthcare. NIH research will continue to be a vital source of knowledge and medical innovation which will sustain the health and quality of life of all Americans.