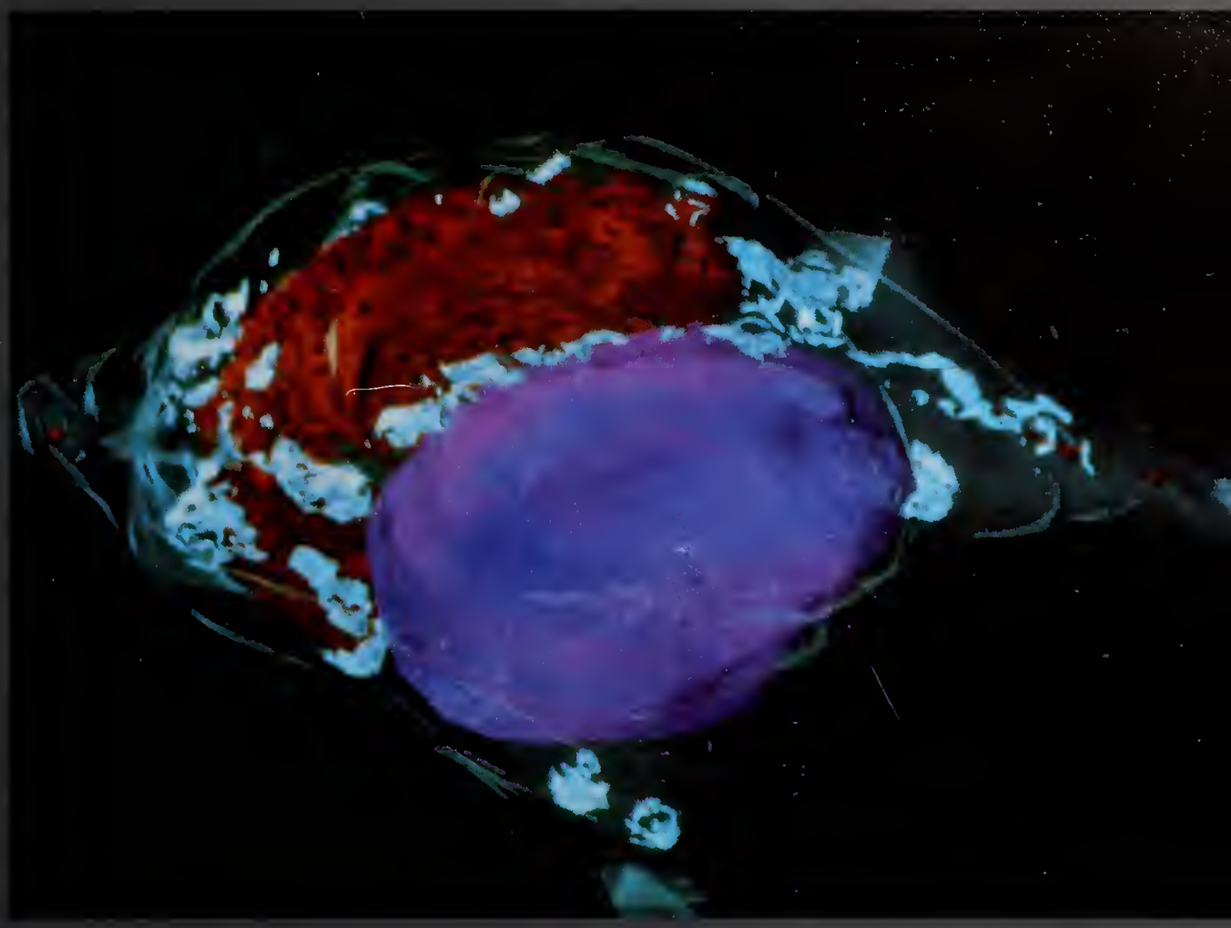

Biennial Report of the Director

National Institutes of Health

1989 - 1990

U.S. Department of Health and Human Services

Public Health Service, National Institutes of Health

The cover photograph depicts a nerve cell from a patient with Alzheimer's disease illustrating the dramatic progress that has been recently made in combining 3D graphics with structural information from electron microscopy. The image shows abnormal structures (large dark area in upper left — called paired helical filaments), which are associated with Alzheimer's disease.

Biennial Report of the Director, National Institutes of Health

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U.S. Department of Health and Human Services
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Executive Summary

Background

The Biennial Report of the Director, National Institutes of Health (NIH), is the third report on the Nation's biomedical research effort submitted by the Secretary of the Department of Health and Human Services to the President and the Congress of the United States, pursuant to Sections 403, 406(g), and 407 of the Public Health Service Act, as amended through December 31, 1989. The report covers the period from FY 1989 through FY 1990.

As specified in the Act, the report is organized around six major topics:

- Advances and opportunities in biomedical research
- NIH research in disease prevention
- NIH health-related behavioral research
- NIH-wide science policy issues
- Activities to improve grant and contract accountability and peer review
- Biennial reports of the NIH institutes, centers, and divisions (ICD's)

Highlights

The third Biennial Report of the Director, NIH, describes NIH activities , while discussing current policies on agency programs and assessing scientific developments and opportunities in important areas of research.

The report reflects the breadth of the biomedical research by both NIH intramural scientists and extramural scientists whose research is supported by the NIH. This research ranges from basic laboratory studies to clinical trials of promising therapies and preventive measures.

In a remarkably short time, the concepts and tools of molecular biology developed by the NIH have diffused throughout the biomedical research community. Biotechnology promises to revolutionize the pace as well as the scope of future biomedical research. A continuation of NIH-supported discoveries in the basic sciences is critical to the long-term success of the American biotechnology industry, as well as benefiting the health of the American economy and the health of its citizens.

During the period covered by the report, our understanding of fundamental biological phenomena has dramatically increased while the time necessary for research results to be transformed into prevention, diagnosis, and treatment of disease has been reduced. With growing knowledge of these underlying biological processes and increasingly more powerful research methods, we are making breakthroughs against an array of diseases that until now have been difficult to prevent or treat. Much work needs to be done.

Examples of advances that provide exciting future opportunities include the following:

- **The human genome project**. The newly created Center for Human Genome Research is mapping and sequencing the human genome and improving genetic research technology. Both of these contributions will make molecular genetics research more effective and save years of tedious work on individual research projects such as determining the genetic factors in

Alzheimer's disease. During the past 2 years the maximum length of deoxyribonucleic acid (DNA) that can be cloned has increased more than twentyfold, from 45,000 to 1 million base pairs of DNA.

- **Molecular genetics**. This science and its applications, such as recombinant DNA techniques, will continue to dominate the biomedical research agenda. Knowledge of the genetic mechanisms involved in disease continues to expand. Molecular genetics enabled (a) the recent isolation of the cystic fibrosis gene, paving the way for new drug development and eventually genetic therapy; (b) the creation of a unified model of the genetic basis of cancer; (c) the transfer of a foreign marker gene to human patients; and (d) the creation of transgenic (genetically modified) animals that can provide unique disease models and critical proteins for research and treatment.
- **Acquired Immunodeficiency Syndrome (AIDS)**. Basic research in virology, molecular biology, and immunology has rapidly resulted in new information about the virus and the disease process. Encouraging developments on the long-term search for vaccines and improved treatments continue. Recently, zidovudine (AZT) has been found to delay the progression of the disease in both symptomatic and asymptomatic persons and a prototype AIDS vaccine has been shown to protect rhesus monkeys from infection.
- **Cardiovascular diseases**. Research supported by the NIH over several decades provided the underpinnings of the 43 percent reduction in the cardiovascular and stroke mortality rate from 1968 to 1988. New findings may expand this remarkable accomplishment. Recently, scientists have mapped the structure of thrombin, the "killer enzyme" involved in 40 percent of all deaths from all causes in the United States, and discovered that pharmacologic and behavioral interventions can cause regression of atherosclerotic plaques.
- **Neurobiology**. Recombinant DNA technology allows the exploration of the nervous system at a molecular level while imaging devices examine the working brain. These techniques have contributed to progress on a diagnostic test for Alzheimer's disease, an animal model for spina bifida, a potential treatment for hepatic encephalopathy, and the discovery of nerve growth factor.
- **Vaccine development**. Vaccines have diminished the incidence of many fatal and disabling diseases. The biotechnology revolution has greatly enhanced NIH's capacity to develop new, safer, more effective, and less costly vaccines. In addition to progress in developing an AIDS vaccine, recent advances include an improved vaccine for pertussis, a potential vaccine for colon cancer, and a more potent class of preventive agents called conjugated vaccines.

Never before has the NIH faced such a wealth of exciting research opportunities with such extraordinary tools. In the future, America will reap an even greater return on its investments in biomedical and behavioral research. This last decade of the twentieth century offers the potential for NIH successes against a broad spectrum of diseases that afflict Americans of all ages, races, ethnic groups, and both genders.

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NIH Director's Preface

The past 2 years have reconfirmed the wisdom of strong sustained funding for biomedical science. Thanks to this public patronage, programs of the National Institutes of Health (NIH) continue to yield research advances that improve the health of people everywhere. During the time period covered in this report, 1989-90, we have witnessed explosive growth in our fundamental understanding of biological phenomena and a progressive shortening of the time it takes for research results to be transformed into practical applications.

As I reviewed this report, I was reminded of the great breadth and depth of research conducted in the NIH intramural laboratories and supported by NIH through grants and contracts awarded to scientists around the country. The highlights selected for this report cover the range of activities from basic laboratory studies to clinical trials and span the spectrum of human biology in health and disease.

The prospects of genetic therapy for human diseases moved several steps closer to reality in 1989, when NIH scientists for the first time transferred cells carrying foreign genes into a human. The gene transfer was carried out in connection with a pioneering approach to cancer therapy that used the patient's own cancer-fighting cells. Initial reports from the gene transfer experiment indicate that a useful new research tool has been created, one that scientists believe might lead to the development of therapeutic measures to be applied in the treatment of diseases such as cystic fibrosis (CF), metabolic deficiencies of the liver, certain cholesterol disorders, and perhaps even acquired immune deficiency syndrome (AIDS).

In another important development noted in this report, two NIH-supported research teams located and sequenced the CF gene on the human chromosome. This finding is an outstanding example of how basic research aimed at answering fundamental questions about living organisms can provide the knowledge needed to solve longstanding medical puzzles. The underlying cause of CF has been the subject of a frustrating search for 50 years. But the identification of the CF gene should allow improved screening for this disorder so that patients can be promptly diagnosed and treated. It also makes CF a prime candidate for new drug development and genetic therapy in years to come.

A leap into the future was taken with the establishment in September 1989 of the National Center for Human Genome Research at NIH. The establishment of the Center reflects the high priority and the increased commitment of funds for this effort to map and sequence the entire complement of genetic material that determines human life. This targeted

effort is expected to have a profound impact on future ability to prevent and treat the more than 3,000 diseases of known genetic origin and to gain a better understanding of other diseases—such as cancer, depression, and hypertension—that have genetic components.

NIH contributions to understanding, preventing, diagnosing, and treating AIDS have been enormous since the disease was first recognized in 1981, and the most important recent advances are noted in this report. For example, findings from two multicenter AIDS drug trials conducted by NIH demonstrated that zidovudine (AZT) delays progression of disease in persons infected with human immunodeficiency virus (HIV) who have not yet developed symptoms of AIDS. Research is moving quickly: This announcement followed on the heels of a finding showing that AZT slows progression of HIV infection in persons with early AIDS-related complex.

As we look at biomedical research highlights year by year, it is easy to lose sight of, and appreciation for, their origins. This report notes many advances that stem directly from the concepts and tools of molecular and cell biology commonly referred to as biotechnology, which has transformed the methods used in biomedical research and spawned a new industry that is beginning to produce better diagnostic materials and drugs. In reading this report I am reminded that NIH—through sustained support for basic research in molecular and cell biology—is largely responsible for ushering in and fostering this new era of biotechnology.

This report not only covers advances and opportunities in biomedical research but also describes some important issues that relate to our mission. I will mention only two. Today, there is general recognition that if the United States is to remain an international leader, we need to encourage our young people to pursue careers in science, engineering, and mathematics. Unfortunately, the number of young people interested in science is falling, as is the number of Americans receiving Ph.D. degrees. This decline will have a devastating impact on the future of biomedical research and subsequently the Nation's health unless NIH and other institutions can reverse the trend.

A second issue relates to the use of laboratory animals in biomedical research. Virtually every major achievement in medical research in the past century has depended in one way or another on the use of animals, and laboratory animals remain vitally important to future progress. Yet in recent years, animal rights groups have increasingly made clear—through sponsorship of unnecessary and highly restrictive legislation, media campaigns, demonstrations, vandalism at research laboratories, and death threats against scientists—that their end goal is to stop *all* research involving animals. More than 40 percent of research projects conducted and supported by NIH involve the use of laboratory animals, mostly rats and mice. NIH efforts in this area must serve two imperatives: (1) its mission to improve the health of the American public and (2) the provision of humane care and use of animals involved in biomedical research.

This Biennial Report of the National Institutes of Health, covering September 1988 to September 1990, is the third such report summarizing recent progress. It was mandated by the Public Health Service Act, as amended through December 31, 1989 to be transmitted to the President and Congress. I see this report as an opportunity to let the broader public—including other Federal agencies; the biomedical research community including business and industry; and the academic, professional, and voluntary

health organizations—know how NIH is expending appropriated money to improve the Nation's health through the support and conduct of biomedical research. This volume includes reports on NIH-wide topics—recent advances and scientific opportunities, disease prevention, health-related behavioral research, NIH-wide science policy issues, activities to improve grant and contract accountability and peer review—and concludes with the biennial reports of the various NIH institutes, centers, and divisions. Five of these chapters are new to the NIH Biennial Report: the report on Health-Related Behavioral Research and the reports of the two newest institutes—the National Institute of Neurological Disorders and Stroke and the National Institute on Deafness and Other Communication Disorders—and two new NIH centers—the National Center for Human Genome Research and the National Center for Research Resources.

I hope that readers will come away from the report as I did, with a sense of awe at what biomedical research has accomplished to date and with anticipation of a future that can barely be envisioned today.

William F. Raub, Ph.D.
Acting Director,
National Institutes of Health

Biennial Reports on

Advances and Opportunities in Biomedical Research

NIH Research in Disease Prevention

Health-Related Behavioral Research

NIH-Wide Science Policy Issues

Activities to Improve Grant and Contract Accountability and Peer Review

Advances and Opportunities in Biomedical Research

The biomedical research knowledge base is growing at a remarkable pace. New, innovative techniques that facilitate the observation and manipulation of biological processes at the molecular level are being employed to map the entire collection of human genes; to determine the order in which the chemical components of DNA are arranged; and to isolate, clone, and study the defective genes responsible for crippling and deadly disease. It is now possible to insert the genetic material of one species into the genome of another. In the future, genetic engineering of this sort may make it possible to induce genes from foreign sources to produce therapeutic protein products in the bodies of patients unable to manufacture sufficient quantities of their own healing proteins. Technologies such as these also might be employed in the future to provide economically efficient methods of producing large quantities of drugs now rendered expensive by standard manufacturing techniques.

Rapid expansion of knowledge also has led to the development of highly sophisticated techniques capable of diagnosing difficult-to-detect infections and to the creation of novel drugs and vaccines.

The following selected advances in biotechnology, neurobiology, acquired immunodeficiency syndrome (AIDS) research, vaccine development, and other selected areas highlight research conducted and sponsored by NIH over the past 2 years. Research in these areas has expanded our overall knowledge of fundamental biological mechanisms and improved medicine's ability to safeguard human health through increasingly sophisticated detection, treatment, and prevention of disease.

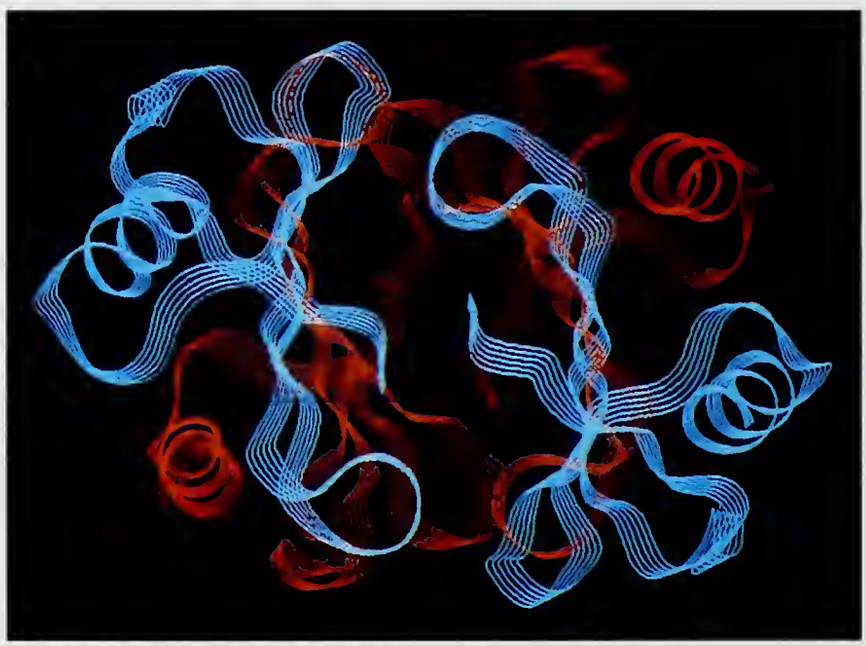
Biotechnology

Laboratory techniques for selectively cutting and recombining DNA, fusing specific cells to produce monoclonal antibodies, and manufacturing synthetic peptides have a broad range of applications. For instance, recombinant DNA techniques are used to develop new drugs and diagnostic kits, produce plants resistant to diseases or herbicides, and clean up the environment. At the same time, these techniques continue to be profoundly important in biomedical research.

In a remarkably short time, the concepts and tools of molecular biology, commonly referred to as biotechnology, have diffused throughout virtually all biomedical research. The following examples are a very small selection from the myriad advances made possible through application of biotechnology. Clearly, the future promises even more dramatic and rapid progress in the treatment, diagnosis, and prevention of disease.

Structure of Blood-Clotting Proteins. There is great interest in producing biologically significant proteins through the use of biotechnology. Many efforts do not succeed, however, because although biologists can engineer genes to produce proteins, they often do not fold into the precise three-dimensional configurations required to make them function properly. For example, developing clinically useful

inhibitors of thrombin would be useful because uncontrolled clotting by this "killer enzyme" is a major factor in approximately 40 percent of all deaths. Recently the three-dimensional structures of thrombin and platelet factor 4, another blood-clotting protein, were determined. Platelet factor 4 has significance even beyond blood coagulation because it belongs to a class of proteins involved in both wound healing and uncontrolled cell growth leading to cancer formation. The ability to reproduce these proteins in their precise three-dimensional configurations should eventually resolve such problems.



The three-dimensional structure of bovine platelet factor 4, which is involved in blood clotting.

Stabilizing Biological Molecules. Proteins can be used for many commercial purposes, including cleansers and pharmaceuticals. One major practical difficulty with proteins in such applications is their frequent instability, both when exposed to high temperatures or other adverse environmental conditions and when being naturally processed and "degraded" (broken down) inside cells. Although many investigators have worked on this problem, until recently no one was able to determine which proteins will be more stable than others and why, much less how to control their stability. Within the past year, however, techniques have been developed to determine how various types of interactions (e.g., hydrogen bonds, hydrophobic interactions, salt bridges) contribute to quantitative and qualitative protein stability. These techniques are expected to be of great value to scientists trying to stabilize biological molecules used in medicine (e.g., vaccines) and to design improved enzymes for use in the pharmaceutical and food industries.

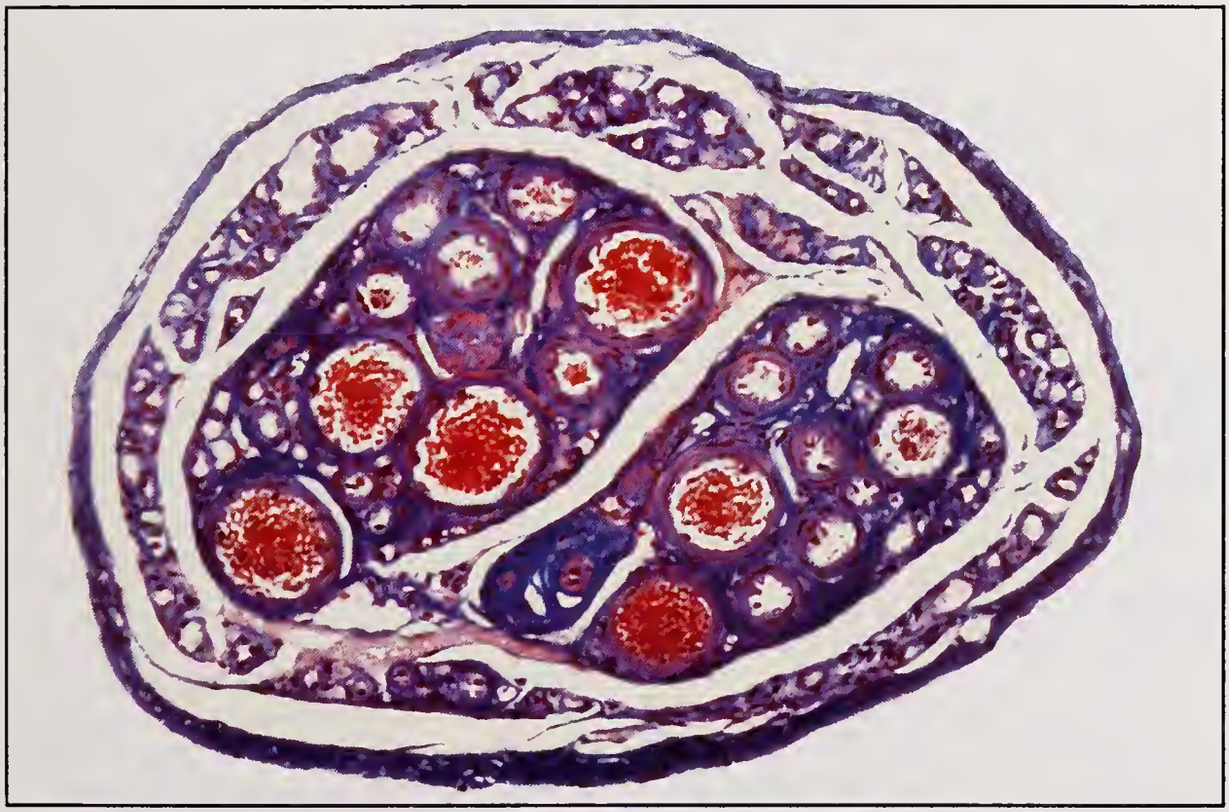
Transgenic Animals. A transgenic animal is one that has had genetic material from another species inserted into its genome. The foreign DNA is then expressed by the animal; that is, the foreign DNA goes on to produce its product, usually a protein, in the body of the transgenic animal. These animals are unique models in which to study many genetic phenomena. An excellent example is the research on regulatory mechanisms called promoters. Promoters control gene expression; that is, they turn genes on and off. Scientists recently developed transgenic pigs that have the gene coding for a specific mouse milk protein and its promoter spliced into their DNA. The pigs later lactated varying levels of the mouse milk protein. Now transgenic cows and goats are being bred with the milk protein and promoter spliced into their DNA. If these large farm animals are able to express the mouse milk protein, they may be engineered in the future to express proteins with therapeutic value, thereby offering an efficient method of producing large quantities of drugs that are prohibitively expensive when manufactured by traditional techniques.

Spotting Difficult-To-Detect Infections. Polymerase chain reaction (PCR) is a rapid, highly specific technique that allows scientists to amplify extremely small amounts of DNA or RNA for study. This technique also affords quick identification of difficult-to-

detect infections (i.e., the DNA of the infectious agent), which should lead to improved treatments for a wide variety of diseases. For example, researchers using PCR have found the proportion of T cells (immune system's lymphocytes) infected with human immunodeficiency virus (HIV, the virus responsible for AIDS) to be 10 to 100 times higher than previously believed. This finding will improve clinicians' ability to assess the relative merits of treatments for HIV infections. In another example, reliable detection of *Borrelia burgdorferi*, the tick-transmitted spirochete responsible for Lyme disease, has been difficult because of low levels of the infectious agent in patients. Tests currently in use may miss as many as 10 percent of infected patients. By using PCR, it is possible to detect the one cell in a million that is infected.

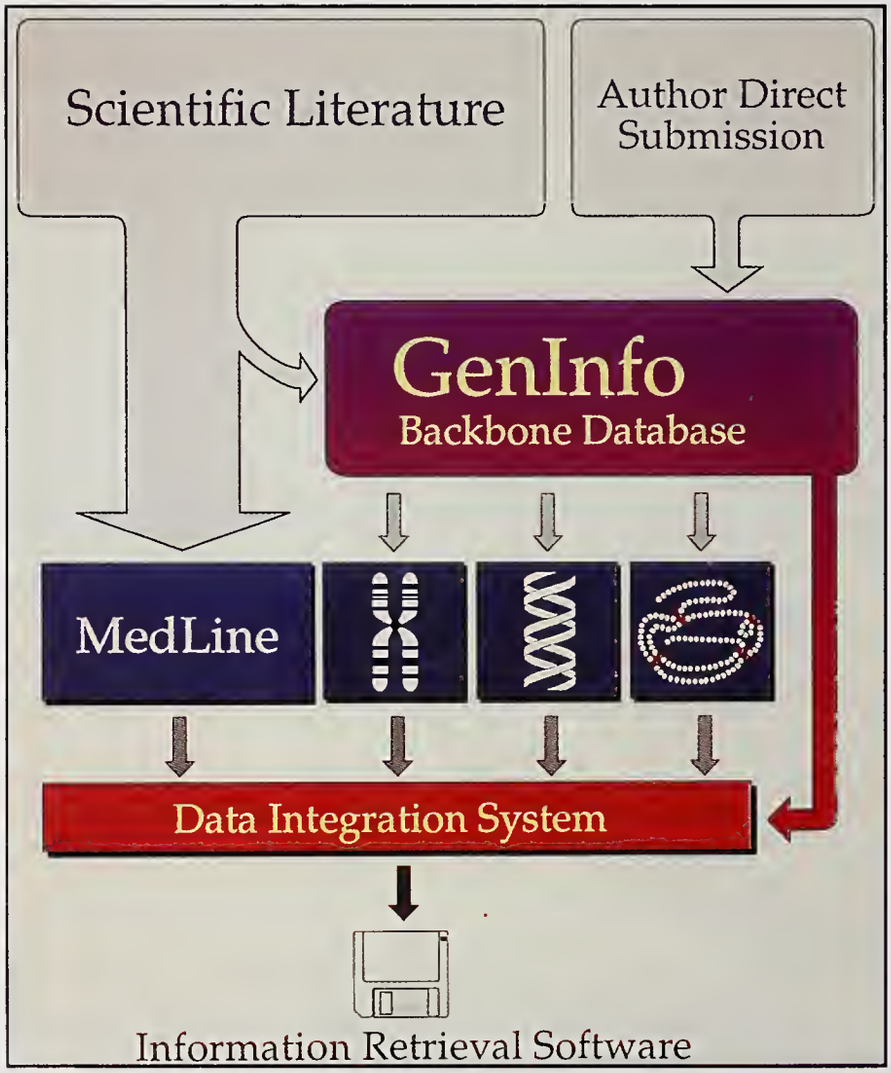
Adoptive Immunotherapy and Gene Transfer. For the first time, scientists have transferred cells containing foreign genes into a human patient. To monitor the results of an experimental cancer treatment, NIH scientists infused patients with tumor-infiltrating lymphocyte (TIL) cells that had been altered by the insertion of a marker gene so they could be tracked in the patient's body. After the TIL cells were reinfused, blood and tumor biopsies were taken at regular intervals to establish where the TIL's went, how well they survived, and what they did. This procedure has proven to be both technically feasible and safe. A significant percentage of the transfected TIL cells localized to the tumor, although many remained in the bloodstream. Future plans include insertion of genes for molecules, such as tumor necrosis factor and interleukin-2, to determine if they will enhance the tumor-killing potential of TIL cells.

Organoids and Gene Transfer. NIH scientists have devised yet another method of transferring desirable genes



Organoid implants in the rat show a large organized network of neovessel formations interdigitated with different cell types. This cross section reveals vascular profiles ranging from capillaries to larger vessels that contain several organized smooth muscle cell layers. The organoid structures were capable of sustaining the biologic function of normal rat liver cells over a period of months.

and their products into mammalian bodies. In this case, an artificial organ called an organoid was implanted into the body of a rat. The organoid consists of rat liver cells growing on a pad of Goretex (nonwoven fibers of expanded polytetrafluoroethylene, the same type used to make plastic rain gear). The cells were encouraged to grow with a growth hormone and engineered to carry an altered bacterial gene, the viability of which could be detected by the researchers. The striking thing about these experiments is that the organoid was infiltrated by new blood vessels from the rat and was able to function for months like a viable body organ, secreting products into the bloodstream via new vasculature. Moreover, the foreign gene remained functional in the cells. Even though all potential problems with the organoids have not yet been solved, studies like these make implantation of therapeutic genetic material into humans a possibility for the future.



NCBI is developing information retrieval software to integrate searches of genetic sequence databases and the scientific literature.

National Center for Biotechnology Information (NCBI) at NIH. To make the large and growing body of information generated by molecular biologists around the world useful for professionals in the biomedical community, the NCBI has been established at NIH, in the National Library of Medicine in accordance with Public Law 100-607. Information access has become an urgent problem. For example, more than 30 million base sequences (from the DNA of plants, animals, and humans) have been reported thus far. Sequence information is of no use if it cannot be easily stored, accessed, and compared. NCBI is beginning to integrate existing data bases and develop new computer programs to analyze them.

Neurobiology

Recombinant DNA technologies allow the dissection of the nervous system at a molecular level while imaging devices scrutinize the working brain. These developing technologies offer endless opportunities to conduct innovative research on the diagnosis, treatment, and prevention of neurological disorders and renewed hope to those who suffer their devastations. Vigorous inquiry is taking place on virtually all neurobiological fronts; some recent scientific advances are discussed in this section.

Diagnostic Test for Alzheimer's Disease (AD). Plaques containing amyloid beta-protein and nerve cell fragments found in the postmortem brains of AD victims are among the major hallmarks of the disorder. Until recently, AD research was hampered because the disease is confirmed only upon the patient's death. However, amyloid

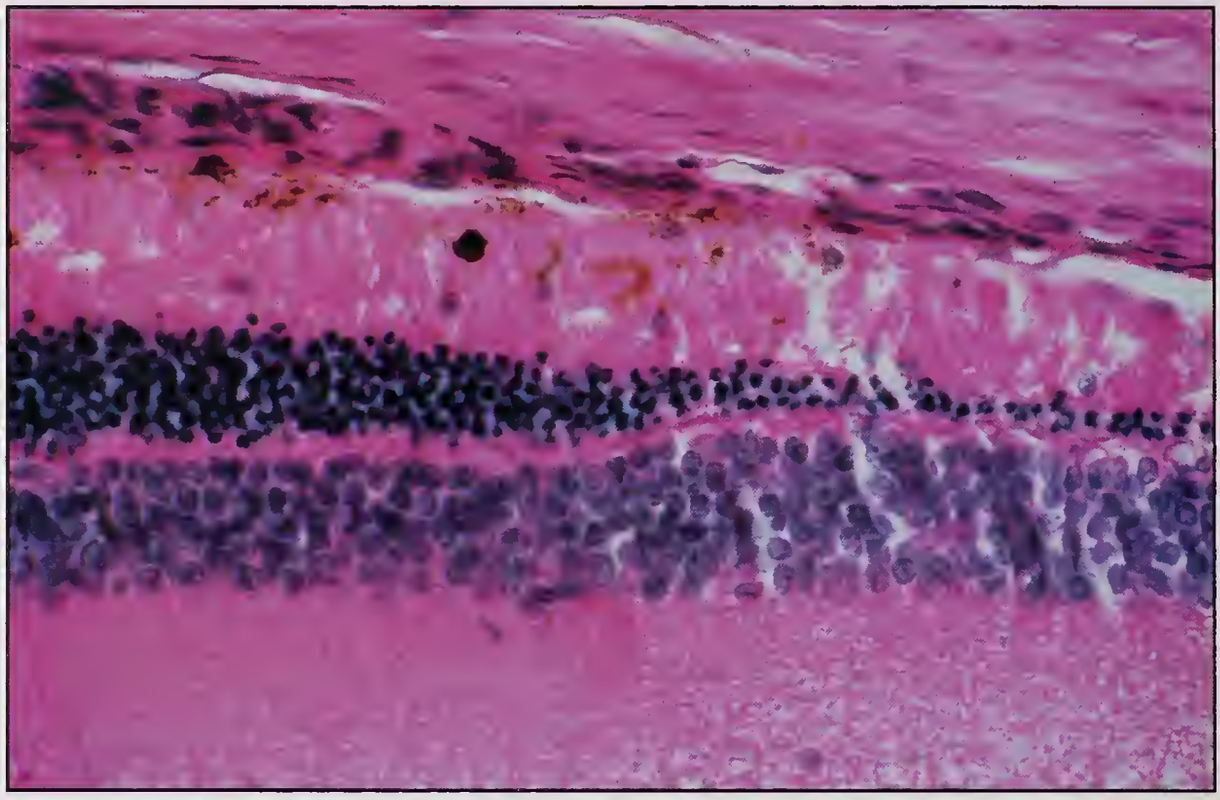
beta-protein was recently found outside the brain: in the skin, tissue just beneath the skin, intestines, and blood vessels of AD patients and in a small proportion of normal persons over age 77. This discovery may lead to the development of a practical diagnostic test for this disease, which afflicts an estimated 4 million Americans. Such a test could also prove useful in monitoring the course of the disease and in judging the effectiveness of experimental treatments. These data suggest that AD may be a widespread systemic disorder and support other findings indicative of a metabolic defect. If so, it is possible that the amyloid beta-protein is transported to the brain from elsewhere in the body. Blocking it from entering the brain might prevent or halt the progress of AD.

Spina Bifida. Malformations of the central nervous system are among the most devastating developmental defects in humans; neural tube defects such as spina bifida are the most frequent and severe. NIH-funded research led to the development of the curly tail mouse mutant, which provides a particularly suitable model for the study of human spina bifida because its deformity closely parallels the condition found in humans. The ability to manipulate the environment of the mouse embryos should provide important insights into the etiology of human spina bifida.

Hepatic Encephalopathy. Each year more than 30,000 Americans die of liver diseases because their physicians have difficulty treating them while they recover from hepatic encephalopathy, a neurological complication of liver failure characterized by mental confusion, even coma. Recently, NIH scientists discovered the process responsible for the syndrome—the accumulation of a naturally produced benzodiazepine-like sedative in the brain and peripheral tissues that depresses brain functions. These findings suggest that an effective means of reversing hepatic encephalopathy would be to treat patients recovering from liver failure with drugs that block molecular receptors to which the sedative must attach to be active. Nearly 80 percent of patients in European studies have thus far been successfully treated with such therapies.

Nerve Growth Factor (NGF). One of the most interesting discoveries of basic neuroscience research is the fact that some brain cells continue to grow and change throughout the life span. This "neuronal plasticity" allows cells to establish new connections with other nerve cells and possibly compensate for those that die during the aging process. The ability of some nerve cells to grow and differentiate depends on the presence of NGF in the brain. New studies suggest that NGF may promote neuron survival by acting on glia, cells that help support nerve cells. NGF also is associated with nonneural tissues such as large blood vessels in the brain, indicating that NGF may play an even larger role in normal nervous system functions. Further elucidation of the role of NGF is needed before clinical applications can be developed.

Cell Replacement Therapy for Inherited Blinding Diseases. A recent research advance raises the possibility of cell replacement therapy for inherited diseases that cause blindness like retinitis pigmentosa. Two separate research teams working independently have successfully transplanted normal rat retinal pigment epithelium (RPE) cells into the eyes of rats with an inherited retinal degeneration. The RPE cell layer acts as an interface between the photoreceptor cells of the neuronal retina and its blood supply. When the RPE cells fail to perform their function, cellular debris accumulates, causing photoreceptor degeneration with resulting loss of vision. In the rat model used in these studies, transplantation of healthy RPE cells abruptly halted degeneration.



Cross section of the retina from a rat with an inherited retinal degeneration 34 days after retinal pigment epithelial cell transplant showing dramatic survival of photoreceptor cells (dark stained bodies across middle of photo) in the area of the transplant (left side of photo) as opposed to the area that did not receive a transplant (right side of photo).

Acquired Immunodeficiency Syndrome (AIDS)

While basic scientists continue to examine the intricate form and function of the nervous system, much of the knowledge gained from such exploration has immediate clinical application. In the case of HIV infection, basic knowledge helps clinicians deal with dementia in AIDS patients.

NIH continues to expand laboratory and clinical research aimed at preventing and treating HIV infection. Basic research in virology, molecular biology, and immunology has rapidly resulted in new information about the structure of the virus, its genetic variability, and the immune mechanisms triggered by infection. Clinical evaluations of vaccines, drugs, and therapies for AIDS-related infections and cancers have also proven valuable. For example, recently conducted clinical trials show that zidovudine (AZT) delays onset of AIDS symptoms in those with early infections. But although drugs promise prolonged life for AIDS patients, scientists will continue to search for improved treatments and ways to stop the action of the virus. Before any new treatments may be offered to the general public, they must be tested for safety and efficacy in clinical trials. The following descriptions highlight a few science advances in the field of AIDS research.

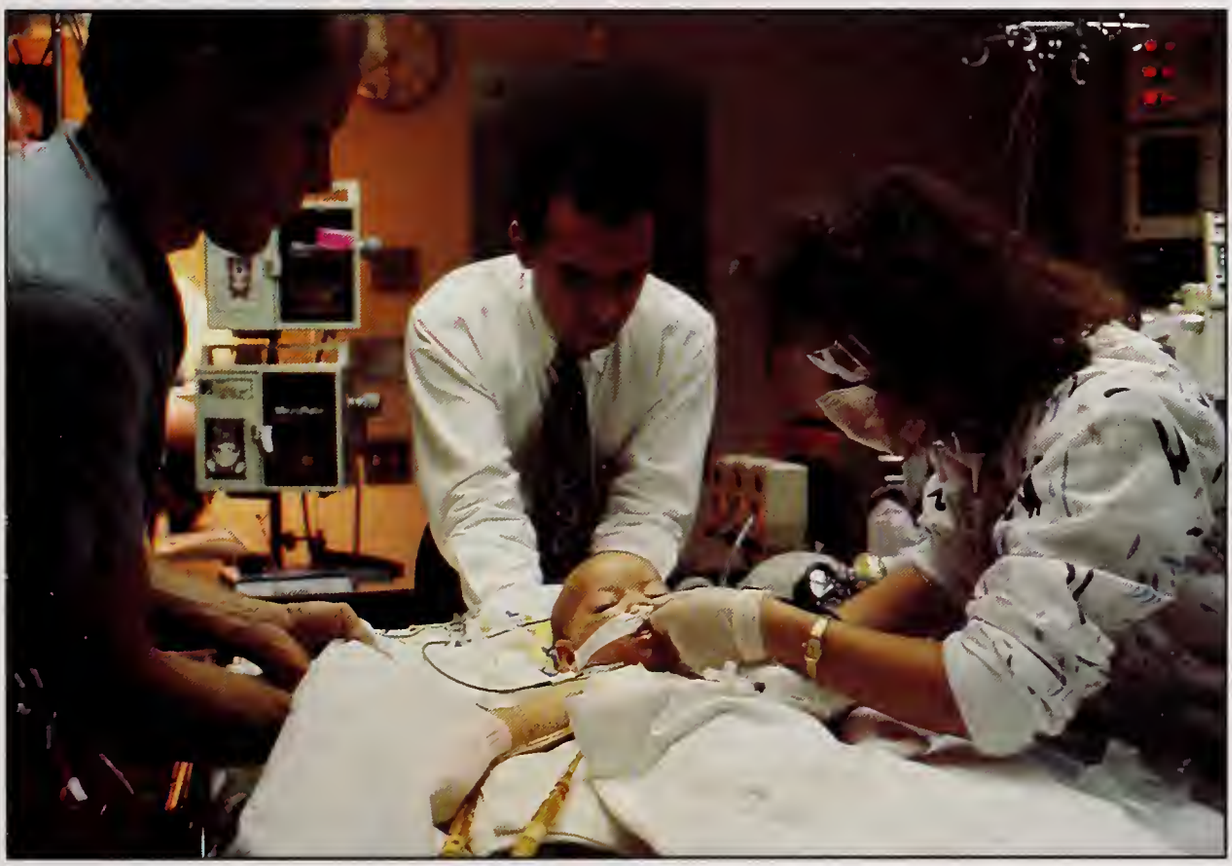
Vaccine for AIDS-Like Disease. Scientists have developed a vaccine that appears to prevent AIDS-like disease in monkeys. The simian immunodeficiency virus (SIV) causes simian AIDS in macaque monkeys and is a close relative of HIV, which causes AIDS in humans. Because there is a strong genetic and functional relationship between SIV and HIV and a physiological similarity between macaques and humans, the SIV macaque model is highly relevant for

AIDS research in humans. Aside from thevaccine development, studies of the SIV macaque model have resulted in several contributions regarding the origins of HIV, AIDS pathogenesis, and drug research.

Mouse Model of HIV Infection. Another good animal model of HIV infection has been recently developed. Homozygous severe combined immunodeficiency (SCID) mice are genetically immunodeficient because of a lack of functional T and B lymphocytes; that is, they are unable to mount an effective immune response to foreign antigens. However, when human lymphoid tissue containing functional lymphocytes is implanted in SCID mice, they develop a competent immune system. These mice then simulate the human immunological response to infection with HIV virus and may serve as a small animal model in which to study the interactions of HIV with the human lymphoid system.

AIDS Dementia. The neurological effects of AIDS, particularly dementia, greatly add to personal suffering. Recent studies are attempting to reveal some of the dynamics involved. For example, patients with AIDS dementia have neurotoxic substances in their cerebrospinal fluid. Monoclonal antibodies to CD4 (the cell receptor by which HIV gains entry to cells) are specifically effective in neutralizing the neurotoxic material present in the cerebrospinal fluid of patients with AIDS dementia. These results improve understanding of AIDS dementia and also suggest possible therapeutic approaches to ameliorating it. Another approach finds the level of glucose metabolism greatly increasing in areas of the brain infected by HIV; however, it declines as dementia progresses.

Viral Enzymes Now Available for Research. To replicate itself, the AIDS virus must synthesize at least three enzymes. One of these is a protease



Clinical center staff positioning x-ray film under pediatric AIDS patient.

required to process newly synthesized viral proteins. This enzyme has now been crystallized and examined by x-ray diffraction, which has permitted the construction of a model. This model shows in three dimensions where each atom is located. Now it may be possible to synthesize compounds that inactivate this enzyme so critical to the growth of the AIDS virus, thereby opening a new front in the war against the AIDS epidemic.

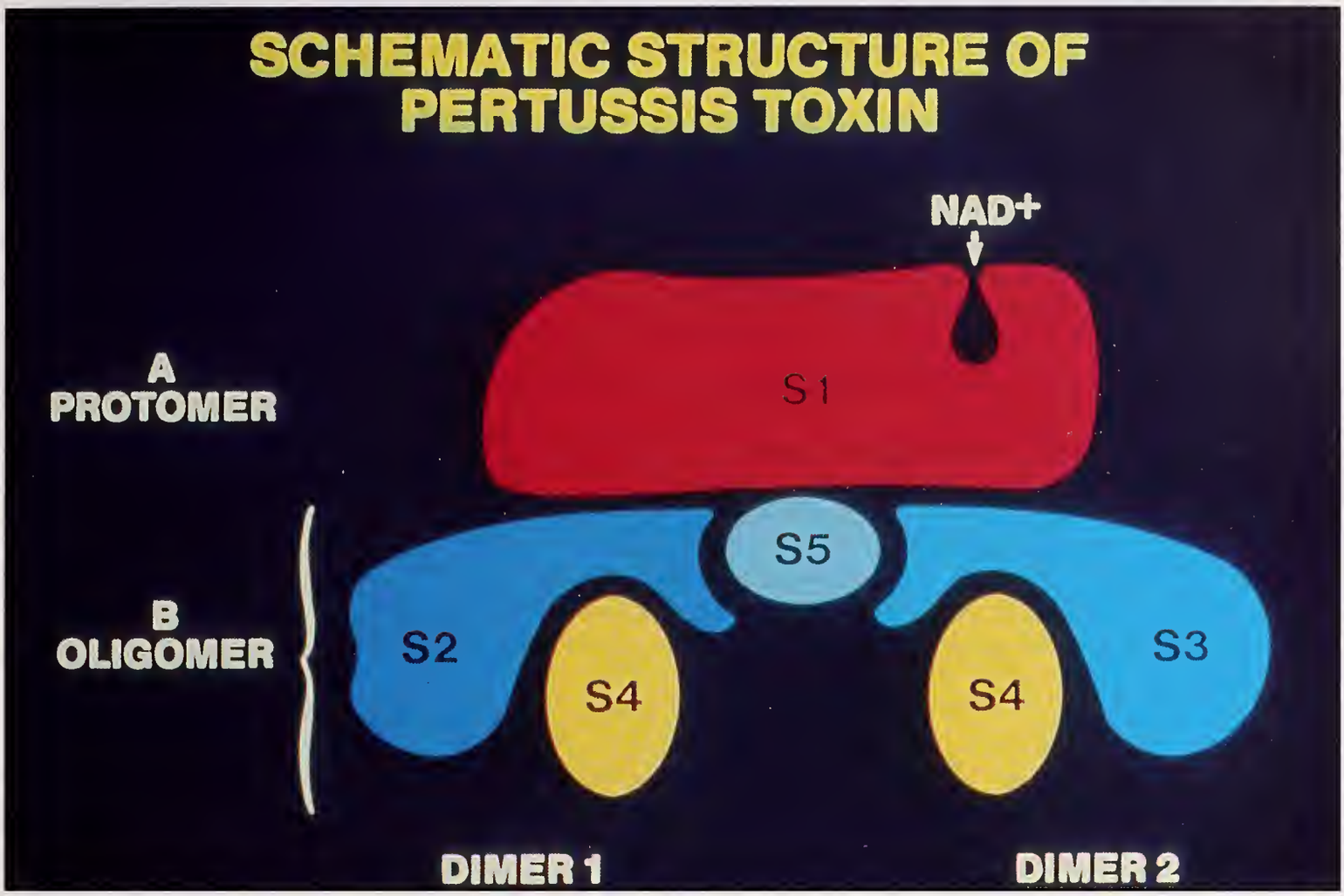
New Blood-Screening Techniques. Promising new testing procedures have been developed to screen donated blood for HIV infection. In one such test, polystyrene beads are coated with HIV proteins capable of binding to HIV antibodies present in test specimen. A fluorescent-labeled immunoglobulin, which binds to the HIV antibody complex, renders the antibodies detectable. This new test has proven more sensitive and specific than currently licensed HIV antibody tests. Another test using PCR technology is capable of detecting one molecule of HIV DNA in 10 microliters of blood.

Anti-AIDS Drugs. AZT is a widely used treatment for AIDS. However, its usefulness is limited by its toxic side effects, particularly bone marrow depression. Investigators have recently identified several related chemicals that may be as potent but less toxic than AZT. One of the most promising, dideoxyinosine (ddI), was developed at the National Cancer Institute (NCI). After obtaining a patent on the molecule and conducting a national competition among potential drug development collaborators, NCI entered into an exchange licensing agreement with Bristol Myers, Inc. Preliminary results suggest that ddI, like AZT, causes a significant rise in the number of CD4 lymphocytes (a prognosticator of improving health) and a significant decline in antigen level (a high level is a marker of viral activity). AZT and ddI are soon to be compared in a large study designed to further investigate their comparative efficacy and long-term toxicity.

Anti-AIDS Drugs and Children. The testing of anti-HIV drugs in children has very high priority because the number of pediatric HIV infections caused by intravenous drug use in women of childbearing age is rapidly increasing (a December 1989 Centers for Disease Control report stated that 1,947 pediatric—under age 13—AIDS cases were reported between December 1987 and November 1989.) A study evaluating continuous infusion AZT in children with symptomatic HIV infection recently has been completed. The therapy was well tolerated, and toxicity was mostly limited to bone marrow suppression. Dramatic improvement in IQ's from baseline occurred in the small sample of children with significant brain dysfunction from HIV infection before treatment. Six children without detectable evidence of brain dysfunction before receiving AZT also showed improvements in their IQ's from baseline. These results suggest that cognitive impairment may be among the earliest manifestations of HIV infections in children. A Phase I study of ddI in children is nearly complete, and preliminary evidence shows that this agent has promising anti-HIV activity in children as well as in adults.

Vaccine Development

Vaccines are suspensions of weakened or killed micro-organisms (whole or portions of bacteria, viruses, or rickettsias) that, when injected into animals and humans, trigger an immune response that protects them from disease. An activated immune system produces proteins called antibodies that are precisely shaped to interact only with specific antigens, molecules intrinsic to the invading micro-organism (e.g., toxins, proteins, polysaccharides). When the antigenic portion of a micro-organism is engaged by an antibody, the micro-organism often is rendered inactive and unable to threaten the individual.



A representation of the structure of the pertussis toxin. The A protomer represents the enzymatic portion of the toxin believed to have the primary responsibility for inducing the toxic effects of the molecule. The B oligomer portion includes five proteins, which are responsible for binding the toxin molecule to the cell and introducing the enzymatic A protomer to the inside of the cell.

Better Vaccine for Pertussis (Whooping Cough). Whooping cough is a respiratory disease contracted by 60 million infants worldwide and resulting in more than 500,000 deaths each year. These children could be protected by vaccination. The current pertussis vaccine that is given in the diphtheria-pertussis-tetanus inoculation is reasonably effective, but it is associated with a significant incidence of side effects, some of which may be serious. The issue of side effects is still under investigation. Although the pertussis portion of the vaccine is made up of whole bacterial cells, investigators believe that antibodies that protect against whooping cough are produced in response to the organism's toxin, not to the rest of the organism. To avoid side effects that may be triggered by those other portions, scientists have produced a vaccine consisting of an inactivated derivative of the toxin that still maintains its immunogenicity (ability to produce an immune response). The vaccine has been tested in adults, 18-month-old children, and infants aged 3 to 12 months, but further clinical trials will be necessary to be entirely certain of its safety and efficacy.

A number of different vaccines against pertussis are being evaluated. More than one type of vaccine may be needed. In one approach to improving the vaccine, investigators have identified mutants of the toxin protein that are potentially nontoxic or less toxic. This discovery raises

the possibility of using proteins that do not require extensive detoxification, yet retain the antigenic capacity of the native protein. Other investigators have succeeded in engineering a cousin of the whooping cough bacteria to produce a nontoxic version of the pertussis toxin that is still capable of inducing immunity. The new toxin is currently under investigation to determine its immunogenicity, efficacy, and safety.

Vaccine for Colon Cancer. The development of a vaccine for colon cancer has yielded encouraging results. Patients whose colon cancer had been surgically removed were assigned to receive either a vaccine made from their own tumor or no further treatment, as is standard practice. Four years of followup have revealed that the patients who received the vaccine had significantly fewer tumor recurrences and deaths than those who received no postoperative therapy. The investigators were thus able to demonstrate a specific immune response in patients who were vaccinated; a large clinical trial is now under way.

Conjugated Vaccines. The *Hemophilus influenzae* type b is a bacterium that causes meningitis and acquired mental retardation in children. NIH scientists pioneered the development of H. flu, a vaccine used worldwide against this micro-organism. Although it is very effective in children, the vaccine has not been effective in infants because of the immaturity of their immune systems and its inadequate response to relatively weak antigens, such as those in H. flu. NIH scientists have now devised a new H. flu vaccine that confers protection from *Hemophilus influenzae* type b bacterium in children as young as 2 to 3 months. The new method binds (conjugates) the bacterium's antigen (a polysaccharide component of the capsule surrounding the micro-organism) to a pertussis toxoid protein, thereby enhancing the antigen's ability to trigger an immune response.

The conjugating concept has also been applied in making vaccines against other bacteria that cause diseases of considerable public health significance, such as the salmonella bacterium (typhoid fever), pneumococcus (pneumonia), *Shigella dysentariae* (epidemic diarrhea), and *Staphylococcus aureus* (life-threatening bacteria found in burn patients, premature babies, and other hospitalized patients). A new vaccine also has been developed to decrease the impact of group B streptococcal (GBS) infection of newborns. The vaccine will be given to mothers known to be GBS positive to boost their antibody levels. Higher maternal antibody levels will confer immunity on the fetus in utero, thereby protecting infants during their first 3 months of life, the period during which this devastating systemic infection is likely to occur.

Other Selected Advances

DNA Greatly Magnified. Scientists have for the first time produced high-resolution pictures of DNA using a technique called scanning tunneling microscopy (STM), which can magnify objects up to a billion times their actual size. The new STM pictures verified what scientists in 1953 deduced about the structure of DNA using x-ray crystallography (a technique that bounces x-rays off crystals, thereby revealing the three-dimensional arrangement of their atoms)—namely, that it is a double helical structure. In the future the new STM technique may allow scientists to directly observe DNA interacting with other biological materials.

Biological Mechanism That Controls Cellular Iron Levels. Scientists at NIH have discovered a novel biological mechanism in the cell that controls iron levels. The mechanism involves a unique protein that responds to fluctuating cellular iron levels by changing its shape. When iron levels become too high, the protein becomes compact; when they fall too low, the protein opens up. This changing architecture is facilitated by

sulfur atoms in the protein that link up when iron levels are high and release each other when they are low. By changing its shape, the iron-sensing protein gives a signal to the cellular machinery responsible for making a protein that absorbs excess iron in the cell. Low iron levels lead to anemia. Too much iron is toxic, particularly in the liver. Understanding these mechanisms will eventually lead to better treatments. Because most proteins depend on sulfur to keep their shape and because shape determines function, this body of research may also prove valuable in the study of other cellular mechanisms.

Osteoporosis. Osteoporosis is a disease of major scientific and public health importance that is responsible for more than 1.3 million fractures of spine, hip, and wrist each year, at a total cost of between $7 and $10 billion. Researchers have demonstrated that decreased production of the active form of vitamin D is related to both osteoporosis and aging. Normally, it is produced in the kidney, subject to regulation by parathyroid hormone and phosphate levels. In osteoporosis, an abnormality in parathyroid hormone secretion has been uncovered, leading researchers to speculate that vitamin D or parathyroid hormone may prove an effective treatment.

Related research has recently demonstrated that administering thyroid hormone decreases bone density, possibly leading to osteoporosis. Because disorders requiring thyroid hormone treatment most often occur in women over age 40, and it is they who are at greatest risk of developing osteoporosis, careful administration of thyroid hormone is crucial. Highly sensitive assays have recently been developed that accurately determine when the necessary amount of hormone has been given.

Soy Formula and Infant Development. Data collection has been completed in the congressionally mandated population-based study of children 9 to 10 years of age who were exposed to a chloride-deficient soy formula during infancy. The children were identified during a mail survey and were given a battery of psychological tests to determine if they had incurred any delay in intellectual development as a result of their exposure to the formula. A comparable group of children matched for age, sex, race, and socioeconomic level was used as controls. The data suggest that the children exposed to chloride-deficient formulas now appear to be performing at levels comparable to their peers, despite early delays in growth and development.

Conclusion

As this brief selection of science achievements illustrates, NIH continues to conduct and support research investigating fundamental biomedical processes and those that apply knowledge generated from such investigations to the formulation of effective clinical interventions and disease preventions. Also evident in these achievements are the large number of studies being conducted at the molecular level on both human and animal models. They are the direct result of recent advances in biotechnology, a discipline that will continue to expand the frontiers of biomedical science.

NIH Research in Disease Prevention

NIH has long been involved in disease prevention and prevention-related research. The mission of NIH is to acquire new biomedical and behavioral knowledge that will lead ultimately to better health for everyone. As a part of that mission, prevention research is intended to protect individuals from acquiring disease and to prevent the progression of disease to disability or death. In fiscal year (FY) 1990 NIH will spend $1.771 billion on prevention-related activities. Figures for FY 1989 prevention research dollars and personnel are presented at the end of this report.

Highlights of the wide spectrum of NIH research activities in prevention are described in the following four categories: basic research, applied research and clinical investigation, intervention studies, and professional and public education. These categories demonstrate the range of efforts aimed at developing effective and safe preventive mechanisms and technologies for translation into health care practice. This report concludes with sections on the Office of Medical Applications of Research (OMAR) and the Division of Nutrition Research Coordination (DNRC).

Basic Research

Familial Hypertrophic Cardiomyopathy (FHC). FHC is a disease of the heart muscle that kills a significant number of young people every year. This abnormality is the most common one found in the unexplained death of young athletes. During the past 30 years, the cardiac features of the disease have been extensively reported, but the etiology and pathogenesis remain obscure. To understand the genetic basis for FHC, workers at Brigham and Women's Hospital in Boston have used genetic linkage analysis to identify the disease locus on human chromosome 14. This first step allowing gene identification, cloning, and sequencing should in turn lead to determining the specific biochemical nature of FHC; the genetic marker may be used to identify asymptomatic individuals at risk for the disease and ultimately may lead to effective prevention.

Relationship of Impaired Smell to Disease Process. The olfactory nerve can serve as a pathway for some pathogens and toxins to enter the brain from the olfactory epithelium. Recent studies in which olfactory threshold and identification tests were used indicate that the vast majority of Alzheimer's and Parkinson's patients have impaired smell function, that this impairment manifests itself before the typical symptoms of the diseases appear, and that there is no difference between the olfactory test results of the two types of patients—a finding that suggests that the two diseases may have a common origin. Of special interest would be determining the etiology of the diseases in the few patients who do not have smell problems. This line of research is being actively pursued because of the important implications it has for the early diagnosis of the diseases and, eventually, for prevention.

Malaria. Using a mouse malaria model, an NIH Fogarty scholar from Sweden, working with scientists at NIH, clarified basic mechanisms whereby immune cells

(CD4 and CD8 T cells) confer protection against malaria parasites. The development of immunity was found to be associated with the stimulation and proliferation of antigen-specific T cells and the secretion of IL-2 lymphokine. Because antigenic components of malaria parasites vary greatly in their ability to induce protective immunity, this information will be valuable in selecting antigens for incorporation in malaria vaccines.

Applied Research and Clinical Investigation

Familial Hypertension and Blood Cholesterol. Hypertension and blood cholesterol disorders aggregate in families. Pathological processes that lead to hypertension, or blood cholesterol disorders, or both, may therefore involve shared genes, shared environmental factors, or a combination. Research on families living in Utah has led to the description of a new syndrome combining hypertension and dyslipidemia that affects approximately 12 percent of patients with essential hypertension. The condition—familial dyslipidemic hypertension (FDH)—has been demonstrated in a limited number of families so far, but the finding does suggest that FDH may be present in 1 to 2 percent of the general population. Pedigree studies such as these are an essential first step in any attempt to understand the genetics of human hypertension or atherosclerosis, knowledge of which will allow strategies to be designed for preventing these widespread diseases.

Acquired Immunodeficiency Syndrome (AIDS). A multicenter drug trial has shown that zidovudine (AZT) significantly delays the progression of the disease in certain persons infected with human immunodeficiency virus (HIV) who have not yet developed symptoms. Another randomized, double-blind trial found that AZT also benefits patients in the early stages of symptomatic HIV infection. These studies have clearly shown the importance of early intervention in HIV-infected persons. Additional research is being conducted to determine if AZT may actually prevent transmission of HIV. Children born to mothers infected with HIV are one of the fastest growing populations of HIV patients. An extensive clinical trial under development will investigate whether HIV transmission can be prevented if a mother is given a dose of AZT just before delivery and her infant is given a dose just after birth.

Alcohol and Cancer. In a nationwide case-control study, heavy use of both cigarettes and alcoholic beverages resulted in greater than 35-fold increases in the risk of oral and pharyngeal cancers. Because previous studies suggested that the risk of breast cancer may be increased with moderate alcohol consumption, a multicenter, population-based, case-control study will continue to evaluate the role of alcohol intake (as well as oral contraceptive use, adolescent dietary patterns, anthropometric measurements, and endogenous hormones) as a risk factor. A cohort of nurses is being followed prospectively to assess alcohol intake, long-term oral contraceptive use, and physical activity on the risk of breast cancer.

Prevention of Diabetic Retinopathy. In 1985 the NIH-supported Early Treatment Diabetic Retinopathy Study demonstrated that using the laser to seal the small leaky blood vessels in the macula reduced the risk of vision loss from diabetic macular edema. In October 1989 the study released data showing that scatter treatment (using the laser to produce burns throughout the retina with the exception of the macula), combined with focal treatment for macular edema when present, was effective in patients with moderate to severe nonproliferative retinopathy or mild proliferative retinopathy preventing severe visual loss. Both treating early and deferring treatment until patients approached or reached a more proliferative stage were

effective in reducing the risk of severe visual loss. If careful followup can be maintained, study investigators concluded that it is safe to defer scatter treatment to a time when retinopathy approaches or reaches the high-risk stage of advanced new vessel growth.

Prevention of Root Caries. Attempts are being made to develop a less time-consuming topical treatment than fluoride to eliminate root and coronal caries in adults. For example, adults older than 60, who are at greater risk for root caries, are being followed for 4 years to assess the use of a daily fluoride in cementum and to assess the use of a glass ionomer (cured restorative material) and visible light-cured microfilled system for restoring carious lesions on the roots of teeth. Other individuals at risk for root caries are those with overdentures, because this technique uses prepared root fragments, which are susceptible to periodontal diseases and caries. For such individuals, an experimental gel is being tested in comparison with a commercial fluoride gel.

Deprenyl Treatment of Parkinson's Disease. This year, an NIH-supported clinical trial revealed that treatment with the drug deprenyl delays the progression of symptoms in patients with early Parkinson's disease and postpones the need for L-dopa therapy. Thus for the first time there is evidence of a drug that can slow the progression of a neurodegenerative disease. Deprenyl was also found to increase significantly the time patients remained gainfully employed, a benefit that will yield increased productivity and annual savings of hundreds of millions of dollars in health care costs. The findings are so striking that the trial was interrupted and modified to provide deprenyl to all patients in the continuing study.

Intervention Studies

Lyme Disease. Lyme disease, which is caused by a tick-borne spirochete, is widespread, with cases reported in the United States, Europe, Asia, Africa, and Australia. In the United States, the number of diagnosed cases of Lyme disease is increasing and appears to be spreading to new areas of the country. Recently birds have been identified not only as important local reservoirs but also as long-distance dispersal agents for infected ticks. It has now been shown that, in addition to white-tailed deer and white-footed mice (the primary tick reservoirs for transmission to humans), migrating birds can also carry infected ticks. This new knowledge about an additional mode of disease transmission is important for prevention and control.

Diet and Chemoprevention in Cancer. A randomized, double-blind, placebo-controlled clinical trial is evaluating the efficacy of nutritional supplements in preventing neoplastic polyps of the large bowel in persons at high risk for this condition. Trial treatments are beta-carotene, vitamin C (ascorbic acid), and vitamin E (alpha-tocopherol). Another group of investigators has recently initiated a randomized trial to evaluate the role of dietary fiber and calcium in subjects at elevated risk of developing colon carcinoma. This trial could lead to a larger scale trial to determine the efficacy of these agents in lowering polyp recurrence rates. In addition, there are two ongoing trials to evaluate the efficacy of chemopreventive agents in preventing the development of invasive cervical carcinoma in women with preneoplastic lesions of the cervix.

Behaviors That Promote Health. Because changes in lifestyle are an important factor in lowering the incidence of many diseases, health-related behaviors need to be identified and reinforced. Studies funded by NIH have identified adult populations at risk for disease (such as smokers), persons at risk for breast cancer, battered spouses, bereaved spouses, and individuals recovering from coronary disease or hip fractures. Research is examining ways to help these groups

improve their self-care and prevent further complications. Two studies are analyzing learned health-related behaviors in adolescents. Factors that influence the choices of adolescents and young adults toward health-risk behaviors such as drug use, smoking, and early sexual activity are being identified. Such studies will enhance the existing knowledge base for prevention and intervention strategies.

Studies of Low Birth Weight and Preterm Labor. Risk factors such as smoking, level of maternal education, restricted maternal weight gain, and a variety of obstetrical conditions do not explain the two-fold increase in incidence in low birth weight among black women as compared to white women in the United States; reasons for large ethnic differences are unknown. To address these disparities, the NIH has launched a major research program in the prevention of low birth weight including a study to obtain data from pregnant women from five ethnic groups and a community-based intervention among predominantly black women in the District of Columbia. Researchers focusing on factors that play an important role in human parturition have found that *Mycoplasma hominis, Chlamydia trachomatis*, heavy smoking, and delivery of a previous low birth weight infant have been associated with preterm birth; and that *Chlamydia, Candida albicans*, and maternal smoking and drinking have been associated with intrauterine growth retardation.

Professional and Public Education

International Network for AIDS Research and Training. NIH has established the International Network for AIDS Research and Training, which links NIH, the Centers for Disease Control, the U.S. Agency for International Development, the World Health Organization, the Global Program on AIDS, and the Pan American Health Organization. The network facilitates the coordination of research and research training needs and the formation of strategies to respond to emerging and unanticipated events.

Sunlight, Ultraviolet Radiation (UVR), and the Skin. Exposure to natural or artificial UVR can cause acute and chronic adverse effects on the skin. Expanded knowledge about the hazards of UVR has been accompanied by improved approaches to photoprotection (possible ways to inhibit or reverse certain chronic effects of sun exposure).

Diabetes, Digestive Diseases, and Kidney and Urological Diseases. NIH supports national information clearinghouses on diabetes, digestive diseases, and kidney and urological diseases, which serve the information and education needs of a broad professional and lay constituency in a number of areas, including disease prevention and health promotion.

Office of Medical Applications of Research (OMAR)

OMAR, in the Office of Disease Prevention, is the focal point for technology assessment and transfer activities that affect prevention and treatment.

One of OMAR's primary responsibilities is to coordinate consensus development conferences, which bring current biomedical research knowledge to bear on controversial issues in clinical practice. In 1989 and 1990, OMAR sponsored 12 consensus development conferences on the following topics: therapeutic endoscopy and bleeding ulcers; oral complications of cancer therapies—diagnosis, prevention, and treatment; sunlight, UVR, and the skin; treatment of destructive behaviors in persons with developmental disabilities; noise and hearing loss; surgery for epilepsy; treatment of sleep disorders of older people; adjuvant therapy for patients with colon and rectal cancer; intravenous immunoglobulin—prevention

and treatment of disease; treatment of early-stage breast cancer; diagnosis and management of asymptomatic primary hyperparathyroidism; and clinical use of botulinum toxin.

In 1990, OMAR also held workshops that addressed health care delivery research using hospital firms; extracorporeal membrane oxygenation; the effects of early dissemination of clinical trials results; and quality-of-life end points in clinical trials.

Division of Nutrition Research Coordination (DNRC)

An important addition to the NIH organization was the establishment of the DNRC in the Office of Disease Prevention in 1988. The new division has enhanced and expanded NIH's goals to effectively coordinate nutrition research programs and training, avoid duplication of research efforts, and speak with one voice in matters of nutrition. In FY 1988, NIH led all Federal agencies in financial support of nutrition research and training with a total of $276 million. A publication prepared by the DNRC and the Nutrition Coordinating Committee (NCC) in 1989 titled *12th Annual Report of the NIH Program in Biomedical and Behavioral Nutrition Research and Training, Fiscal Year 1988* described current NIH-wide nutrition activities. The DNRC was extensively involved in the review and coordination of a major portion of the chapters in the recent *Surgeon General's Report on Nutrition and Health*, which summarized research on the role of diet in health and implications for dietary guidance, programs and services, and research and surveillance. The DNRC serves as executive secretariat to the Interagency Committee on Human Nutrition Research (ICHNR) and played a major role in the ICHNR's Fourth Conference on Federal-Supported Human Nutrition Research Units and Centers on Nutritional Function and Nutrient Interactions and Toxicities, held in February 1989.

In 1990, the DNRC/NCC sponsored a series of seminars to focus attention on obesity, one of the most prevalent diet-related problems in the United States. Topics included obesity and associated risk factors for disease; malignant obesity: pathophysiology and treatment; racial and ethnic differences in obesity and associated cardiovascular morbidity; and measurement of total body fatness.

NIH Prevention Research Dollars and Personnel, 1989

Institute	Prevention research dollars (in thousands)	Prevention personnel (full-time equivalents)
National Institute on Aging	131,996	64
National Institute of Allergy and Infectious Diseases	134,167	171
National Institute of Arthritis and Musculoskeletal and Skin Diseases	72,167	63
National Cancer Institute	481,687	812
National Institute of Child Health and Human Development	181,895	169
National Institute on Deafness and Other Communication Disorders	18,879	0.5
National Institute of Dental Research	27,937	102
National Institute of Diabetes and Digestive and Kidney Diseases	124,200	120
National Institute of Environmental Health Sciences	187,184	558
National Eye Institute	48,648	50
National Institute of General Medical Sciences	3,962	1
National Heart, Lung, and Blood Institute	179,510	189
National Institute of Neurological Disorders and Stroke	49,228	169
National Center for Nursing Research	5,447	3
John E. Fogarty International Center for Advanced Study in the Health Sciences	—	5
National Center for Research Resources	60,325	0.0
Total	1,707,232	2,476.5

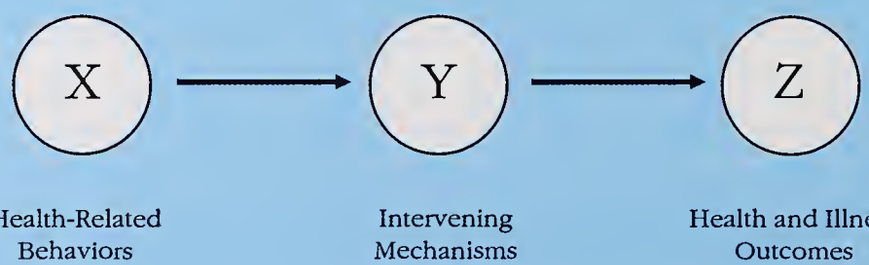
Health-Related Behavioral Research

Social and behavioral sciences are making increasingly important contributions to understanding the promotion of health, functioning, and quality of life; the prevention, treatment, and cure of disease; and rehabilitation. These contributions stem from the identification of lifestyle and behavioral factors as major contributors to over half the deaths in the United States. Many medical problems, including heart disease, cancer, and acquired immunodeficiency syndrome (AIDS), are now known to be influenced by habits of living, social environments (work, family, community), and psychosocial "stress."

NIH has a long history of support for health and behavior research, manifested recently by its cosponsorship of the Institute of Medicine's 1982 report titled *Health and Behavior: Frontiers of Research in the Biobehavioral Sciences;* development of the proposed Public Health Service Initiative on Health and Behavior (1984); and establishment of the NIH Working Group on Health and Behavior (1981) to coordinate activities and to make recommendations to the Director, NIH. Most research components of the NIH have programs that support or conduct health-related behavioral research, and each establishes its own plans and funding levels. Overall, NIH's support for health and behavior research and training (both intramural and extramural) was $258 million in fiscal year 1989 (about 4 percent of the total NIH research and training budget).

A wide range of NIH-supported studies deals with three types of processes linking behavior to physical health and illness (see the heuristic diagram): identification and distribution of psychosocial risk factors (X-Z); development, maintenance, and change of health-related behaviors (X); and basic biobehavioral mechanisms (Y).

Simplified Heuristic for Organizing Health-Related Behavioral Research



Examples of these three types of research are reported in the following paragraphs. The overall goal of NIH is to understand how behavior, biology, and health influence one another and to develop behavioral interventions for preventing and treating illness and promoting health. Health-related behavioral research concerned directly with disease prevention and health promotion is reviewed in the section titled "NIH Research in Disease Prevention."

Identification and Distribution of Psychosocial Risk Factors

The first type of NIH research activities focuses on correlations among (a) particular behavioral, social, and cultural factors and (b) various aspects of health and functioning. Such research also considers the prevalence of such factors in different population groups. Examples are as follows.

AIDS and Other Sexually Transmitted Diseases (STD's). Because AIDS could be a preventable disease, behavioral research is essential for assessing risk factors for infection and for tracing the natural history of the disease. For example, in a cohort of more than 5,000 homosexual and bisexual men studied since 1984, neurological and psychological abnormalities associated with human immunodeficiency virus (HIV) infection have been identified, and behavioral changes in response to the growing epidemic have been quantified. This study found no significant decline in the neuropsychiatric status of HIV-infected individuals before the onset of symptoms of the disease itself—a finding with widespread policy implications for asymptomatic HIV-infected people. In another example, multicenter collaborative studies of perinatal and heterosexual transmission have just begun to accrue patients in order to examine HIV infection and changes in immune function, and risk factors such as specific sexual practices and other behaviors (e.g., intravenous drug use). Further research is needed on STD's in general, which cause extensive morbidity, which are increasing among certain population groups, and which are a cofactor in HIV transmission. An important cross-sectional survey of U.S. adults, if approved, can provide critical national data on the prevalence and distribution of sexual practices conducive to AIDS and other STD's and is essential as a baseline for intervention research in this area.

Risk Factors in Old Age. Even in old age, behavioral risk factors make a difference in morbidity and mortality. For example, one 17-year study is investigating behavioral and social risk factors among people who were aged 60 or older when the study began. Each of several factors—current smoking, lack of leisure-time physical activity, poor dietary habits, and social isolation—increases the risk of mortality by about 50 percent over refraining from smoking, engaging in physical activity, maintaining healthful dietary habits, and being socially integrated, respectively. Moreover, examination of the natural history of such risk factors indicates a high degree of clustering. For example, those older smokers who quit showed significantly less decline in physical activity than those who continued to smoke. Additional research is planned to examine more fully this clustering of social and behavioral risk factors, their differing effects on men and women, and changes in their causes and consequences.

Coronary Heart Disease (CHD). Although personality and emotional factors have long been linked to CHD, only recently has evidence emerged that relates specific characteristics of behavior, personality, and environment. In particular, several studies pinpoint hostility

and lack of social support. For example, the Multiple Risk Factor Intervention Trial indicates that hostility is associated with CHD; and a significant relationship between hostility and severity of CHD has been found in patients undergoing angiography. Several other studies have demonstrated a relationship between degree of social support and existence of CHD risk factors as well as illness and death from CHD. Social support also has been found to interact with other factors (e.g., stress and perceived control) to influence the likelihood of CHD and death. Further knowledge of the bio-behavioral mechanisms of various emotional, dispositional, behavioral, and environmental factors may lead to more effective methods to reduce CHD risk.

Development, Maintenance, and Change of Health-Related Behaviors

A second type of NIH-supported studies encompasses research on particular health-related behaviors (such as smoking, sedentary life style, and inadequate communication with care providers) and the antecedent factors establishing, maintaining, and altering these behaviors. Here, as shown in the following examples, the goal is to understand how the mechanisms by which behaviors correlated with negative health and functioning outcomes could be prevented or changed and how behaviors correlated with positive outcomes could be supported.

Smoking Cessation. Despite dramatic declines during the past decade, cigarette smoking continues to be a significant cause of cardiovascular disease, stroke, and atherosclerotic peripheral vascular disease. Smoking also is the major cause of chronic obstructive pulmonary disease in the United States, far outweighing other contributing factors. Although Americans recognize the risks of smoking and try to stop, many relapse. Studies, therefore, are focusing on understanding the factors contributing to relapse, on developing cessation programs tailored to specific individuals and population groups, and on the biologic and behavioral effects accompanying tobacco use. Resultant data can eventually be used in more effective smoking cessation and relapse prevention programs. For example, specific smoking cessation programs are being designed for patients with cardiovascular disease, who often continue to smoke even after diagnosis of heart disease, and for minority populations, who have been less influenced by the public service messages that have resulted in decreased smoking among whites.

Adherence to Treatment Among Adolescent Diabetics. Because treatment for diabetes involves a lifelong regimen of self-care, it is critical to understand how such behaviors can be fostered and maintained. Since 1981, a longitudinal assessment of the impact of psychosocial and stress dimensions on outcome patterns of diabetic adolescents (aged 11 to 13 at the beginning of the study) has been under way. Recent analyses show that overall compliance with the prescribed regimen, as measured by hemoglobin A1c levels, deteriorated as the children aged. Patients whose parents had a history of separation or divorce had worse control than other patients. Thus, life stresses may be important markers for adolescents who are at risk for either dropping out of medical care or maintaining poor glycemic control and compliance.

Flexibility of Older People's Health-Related Behaviors. Contrary to popular assumptions that older people are neither willing nor able to change their behaviors, research shows that older people can be successfully recruited into health promotion programs (self-care, exercise, and falls-prevention programs); behavioral

change programs can indeed be effective in modifying individual behaviors and lifestyles (increased physical and social activity, awareness of environmental hazards); older people comply no less with medical regimens than younger people; and organizational strategies (changing staff-resident interaction patterns in nursing homes) can be designed to reinforce individual behavior change. Plans call for developing and testing psychosocial interventions in areas of special relevance to older people (e.g., falls and injuries, breast cancer screening, harmful dietary practices).

Basic Biobehavioral Mechanisms

A third type of NIH-supported research aims to specify the mechanisms or processes through which behavior influences health and illness and thereby to clarify how physiological processes might explain the correlations identified by behavioral epidemiology. NIH, by building on its solidly established base of biomedical and behavioral research, is optimally situated to achieve increased understanding of these biobehavioral mechanisms.

Depression and Rheumatoid Arthritis. Recent research is showing that, in patients with rheumatoid arthritis, depression is correlated with pain, functional limitation, and disease activity. These results are particularly interesting because other research (using a rat model) has demonstrated a defect in the hypothalamic-pituitary-adrenal-immune axis that correlates with susceptibility to inflammatory arthritis. This defect is an inability to produce corticotropin-releasing hormone in response to stress and inflammation, resulting in a deficient output of corticosteroids from the adrenal. Because corticosteroids are the most potent anti-inflammatory agents in the body, this deficiency is presumably responsible for unchecked inflammatory arthritis in the rat. Although the extension from the animal model to the human has yet to be made, corticosteroids are known to have antidepressant effects in humans. Thus, depression in patients with rheumatoid arthritis may be related to a deficiency of corticosteroid response. Much work remains to be done on the origin and role of depression in patients with rheumatoid arthritis.

Blood Pressure and Reactions to Stress. Knowledge of the mechanisms by which the brain controls cardiovascular function has increased substantially in recent years. Although it is known that the release of adrenocorticotropic hormone regulates the body's response to stress, this response has been only recently found to be modulated also by internally produced opioid neuropeptides, which diminish pain perception. Young adults at risk for later development of hypertension are reported to show a pattern of exaggerated circulatory, sympathoadrenal, and behavioral responses to stress in both laboratory and natural settings. The precise biobehavioral mechanisms of these responses remain to be identified, but recent findings suggest that defective opioid-mediated sympathetic inhibition may play a major role.

Research on the developmental pathophysiology of hypertension may lead to improved behavioral therapies to reduce high blood pressure. For example, behavioral techniques have been developed for lowering blood pressure and/or reducing the need for medications in middle-aged as well as elderly patients. The study of the physiological mediation of behavioral influences on blood pressure has been facilitated by the development of a portable system for continuous, noninvasive monitoring of respiration in ambulatory patients. Based upon these behavioral techniques and the portable monitoring system, researchers are now investigating the interactions of stress and

salt intake in the regulation of blood pressure and its mediating physiological mechanisms.

Social and Endocrine Effects on Immune Function. Recent research on monkeys and humans contributes to the view of the immune system as a major integrative network involved in biological adaptation. This research comports with a large number of clinical and experimental studies showing that psychological variables and stress produce specific endocrine and immune responses. By interacting with other physiological systems, such stimuli induce hormonal responses and immune alterations that may increase susceptibility to disease.

Current studies of social and endocrine effects on immune function in monkeys are based on observations providing evidence that factors inherent in typical housing environments can alter immune function and susceptibility to infection. Both clinical and experimental data show that endocrine variables alter immune function and responses. Monkeys housed socially are exposed to a variety of psychosocial stimuli that may have important consequences for immune function. Such monkeys exhibit a social organization that includes dominance and relatively high rates of social conflict and antagonism, and consequently, stress-inducing events; thus they provide an ideal setting for the systematic study of these phenomena and the testing of hypotheses about how stress interacts with the immune system in humans.

These studies, which are expected to contribute a better understanding of the increasingly important area of psychoneuroimmunology, exemplify the broader range of health-related behavioral research supported by NIH.

NIH-Wide Science Policy Issues

Even as biomedical research continues to advance and flourish, a number of issues related to the conduct of biomedical research have emerged and need to be addressed if the country is to retain its position of leadership in dealing with human disease and disability. The issues discussed in this section are Department of Health and Human Services (DHHS) secretarial initiatives. Some of these issues focus on strengthening various components of the research infrastructure; others relate to attracting minorities, women, and the disadvantaged to biomedical science careers at NIH. These issues in turn have spawned an interest in research training, science education, and science literacy. Still other issues relate to enhancing medical rehabilitation research at NIH and assuring humane care of animals used in research.

In examining some of these science policy issues, NIH leadership seeks advice from a variety of sources that are important components of the policy development process, such as the Advisory Committee to the Director (ACD), NIH; other chartered committees; and where appropriate, expert consultant panels. NIH is also addressing other important issues not discussed in this report, such as recruiting and retaining senior NIH scientists, rehabilitating the NIH campus infrastructure, promoting the future scientific growth of biotechnology, and dealing with scientific misconduct.

Careers in the Life and Biomedical Sciences for Minorities, Women, and the Disadvantaged

Issue

How can NIH recruit and retain increasing numbers of minorities, women, and disadvantaged into biomedical and life sciences careers?

Background

The Secretary of DHHS and his predecessors have long been concerned about the underrepresentation of minorities in the life sciences and in biomedical research. NIH has demonstrated its commitment to the recruitment of underrepresented minorities into life sciences careers since the early 1970's with programs such as the Minority Biomedical Research Support Program, established in 1971, and the Minority Access to Research Careers Program, established in 1972. Other NIH programs aimed at recruiting and supporting minority populations include the Research Supplements for Minority Undergraduates; the Comprehensive Minority Biomedical Program; the Minority High School Student Research Apprentice Program; and the Minority Institutional Research Training Program.

Current Status

NIH is making a concerted effort to increase the numbers of underrepresented

minorities, women, and disadvantaged persons in its work force by reaching potential candidates at the earliest stages of their careers to inform them of opportunities at NIH and by developing the careers of persons currently in the NIH work force. The Postdoctoral, Predoctoral, and Summer Intramural Research Training Awards Program is one program for doing so. Other programs being developed include an undergraduate scholars recruitment program and a physician loan repayment program. In addition, NIH has supported a series of national workshops and symposia designed to develop programs to recruit and support minorities in research and research training, especially Hispanic-Americans, Native Americans, and Alaska Natives.

Next Steps

The impact of these programs on the number of minorities, women, and disadvantaged persons entering biomedical and life sciences careers will be measured through a series of evaluation studies. In addition to these studies, a data matrix is being developed to track the number of underrepresented minorities, women, and disadvantaged persons, as well as the factors that influence their decision to prepare for careers in the biomedical and life sciences.

Research Training

Issue

There is continuing concern that not enough professional doctorates are choosing biomedical research as a career.

Background

In April 1989, the Director, NIH, established a task force to review NIH biomedical research training programs that develop physician scientists, areas of research training currently not adequately addressed, and research training programs for nonphysician scientists.

Current Status

The task force recommended improving research training for professional doctorates by providing more opportunities for early recruitment into research careers; requiring a minimum of 2 years for appointments to institutional training grants, with the opportunity of obtaining up to 3 years of training through individual fellowships or career development awards; and integrating research training with clinical certification requirements. As a further incentive, the task force recommended seeking a revision in the National Research Services Award payback requirement to forgive the cost of the first year of training upon completion of the second.

The task force also recommended that NIH develop advanced programs of study in new areas, such as clinical trial design and methodology, biostatistics, and epidemiology, and periodically evaluate the need to provide opportunities for research training in emerging areas.

The task force urged that NIH increase stipends to match house staff officer salaries, implement a two-tier cost-of-education allowance (one for private schools, another for public institutions) as a mechanism of controlling tuition reimbursement, and develop systems for routine monitoring and evaluation of the effectiveness of research training programs.

Next Steps

An NIH implementation committee has already developed a strategy to obtain the research community's advice regarding legislation necessary to implement task force recommendations and the financial impact of such legislation.

The first stage of public discussion of the recommendations was scheduled at the January 1990 advisory council and advisory board meetings. Council input was requested on several key issues, particularly on the impact of fiscal planning recommendations, that is, the potential tradeoff between numbers of trainees and costs. Comments from the various council members will be compiled and presented to the Institutes, Centers, and Divisions (ICD) directors. Additional guidelines and position papers are being prepared to guide the implementation of the task force recommendations.

Scientific Literacy and Biomedical Science Education

Issue

How can NIH contribute to national efforts to cultivate biomedical science literacy and to ensure a pool of well-educated biomedical research scientists and technical personnel to meet current and future needs?

Background

In 1986, NIH began to focus attention on the factors affecting the supply of future biomedical researchers by establishing an advisory group to develop plans for attracting students into health research careers.

In 1989, the Secretary, DHHS, developed a biomedical research initiative with five overarching goals, one of which was to cultivate scientific literacy and improve biomedical science education. The Assistant Secretary for Health (ASH) established the Working Group on Biomedical Science Education with a mandate to develop strategies for increasing scientific literacy and to ensure an adequate pool of well-trained biomedical scientists. NIH was designated the lead agency, and the associate director for science policy and legislation was appointed as chair of the Working Group, whose report, submitted to ASH in December 1989, set forth a broad set of objectives, options for action, and strategies to accomplish the two goals.

Current Status

An action plan based on the report and the agency's response to its recommendations was prepared in February 1990. To assure measurable outcomes, each recommendation contained in the report was subsumed under one of the two strategies as either an objective or a deliverable. Both the report and the action plan were accepted by ASH; implementation began in April 1990. A PHS Life Sciences Education and Science Literacy Board, cochaired by the Director of NIH and the ADAMHA Administrator, has been established on a permanent basis to carry out the PHS science education plan. These activities will also be coordinated with other Federal agencies through the Education and Human Resources Committee of the Federal Coordinating Council on Science Engineering and Technology.

Next Steps

NIH will continue its activities to attract young people into biomedical and life sciences careers, including the development of education curriculum supplements; the planning of symposia aimed at the education, recruitment, and retention of minorities in the health sciences; and the proposed establishment of a graduate university at NIH offering research training opportunities. To support these actions, NIH has identified a program director and an organizational locus for its biomedical and life sciences education effort in the Office of Science Policy and Legislation. In addition, the NIH Director's Advisory Group on Biomedical

Science Education continues to advise on NIH initiatives.

Extramural Research Facilities

Issue

What is the current status of extramural biomedical research facilities?

Background

Scientific investigation requires modern facilities in good condition. When this need is compromised, research inquiry is constrained because financial resources must be invested before opportunities can be adequately addressed. According to a 1988 study, there are 10 separate NIH construction authorities, only one of which is currently being funded. The 1988 study also underscored the need for a national strategy on extramural biomedical research facilities.

In January 1989, NIH, in conjunction with the National Science Foundation, released the results of a national survey of academic institutions, research organizations, and hospital research facilities. Thirty-six percent of the research space was reported to be in inadequate condition, with only 28 percent suitable for the most sophisticated research. In addition, there were large backlogs of deferred construction and renovation. The survey report noted that inadequate Federal support, increased costs, regulatory and safety requirements, and changing technological needs have all put pressure on the facility infrastructure.

Current Status

In February 1990, a joint report of NIH and the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA) recommended $150 million for an NIH-ADAMHA facilities construction and renovation grant program to broaden the base of science among institutions currently engaged in biomedical and behavioral science research, with set-asides for institutions with predominantly minority enrollments. It also recommended raising the limit on tax-exempt bonds to $300 million.

Next Steps

DHHS is currently reviewing the NIH-ADAMHA proposals. NIH also has submitted a more general legislative request to DHHS for NIH-wide construction authority, and similar legislation has been introduced by Senator Kennedy (D-MA).

Medical Rehabilitation Research

Issue

How is NIH strengthening the scientific environment for medical rehabilitation research?

Background

NIH has a significant investment in basic and clinical research aimed at improving the quality of life for persons with disabilities. Although there are some definitional problems involving medical rehabilitation research that could affect current NIH estimates of research dollars expended in this area, research has increased from $102.1 million in fiscal year (FY) 1987 to $124.9 million in FY 1990. Medical rehabilitation research is supported by 13 components of NIH and the Department of Rehabilitation Medicine in the NIH Clinical Center. Existing legislative authority places these research programs as integral parts of the specific research responsibilities of the individual NIH institutes to avoid fragmentation of the research effort and to take full advantage of scientific advances made in related areas.

Current Status

For the second year, legislation on this issue has been introduced in response to efforts by the medical rehabilitation research community to establish a distinct entity for this area of medical research at NIH. One version of this legislation calls for the establishment of a national center for medical rehabilitation research in the National Institute of Child Health and Human Development (H.R. 3819). Another bill would establish a free-standing national center for medical rehabilitation research (S. 1393).

The NIH response to the legislative interest and the concerns of the research community was to convene an 18-member panel of consultants to the ACD, NIH, to receive testimony from the medical rehabilitation research community; to assess the current administration of physical medicine and rehabilitation research at NIH; and to suggest ways to ensure continued progress in this area. In presenting its recommendations, the panel urged that the research agenda, priorities, and mission for this area of research be identified expeditiously, and determined that such a clarification is an important step before developing a distinct organizational locus. After reviewing the report of the panel, the ACD concluded unanimously that NIH should develop a research agenda and mission statement to guide this area of medical research and that an immediate effort to create a free-standing center was premature and could dilute, rather than enhance, medical rehabilitation research efforts at NIH.

Next Steps

As a followup to the panel and ACD meetings, NIH has launched a policy initiative to focus on the development of a comprehensive research plan in medical rehabilitation research; it should be ready for broad dissemination by fall 1990.

Economic Yields of NIH Biomedical Research Support

Issue

What are the economic yields from NIH-supported biomedical research?

Background

Many of the important contributions of NIH-supported biomedical research are well known, such as the cadre of trained research manpower, the long list of Nobel Prize winners, the significant breakthroughs in knowledge about the fundamental processes of life and disease, and the thousands of lives saved or improved. Less well known, but no less significant and important, has been the reduction in costs of illness resulting from health care innovations made possible by NIH-supported applied research and clinical trials (basic research is not included in this assessment). This reduction represents economic yields of paramount importance to a society struggling with rising health care costs and budgets.

Current Status

For some time, the Research Benefits Assessment Program of the Office of the Director, NIH, has been investigating such cost savings. In collaboration with the ICD's of NIH, 26 advances leading to reduced treatment costs, morbidity, and premature mortality have been identified to date. These in turn have been translated into significant economic yields.

Health care advances take many forms, such as a new hepatitis B vaccine, laser photocoagulation treatment of diabetic retinopathy, mass screening for neonatal hypothyroidism, and decreasing surgery for tonsillectomy. All such examples can be grouped into diagnosis and screening, new therapies, prevention, or evaluation of existing practices.

The total NIH investment in applied research and clinical trials across all the examples and years amounts to approximately $800 million in 1989 prices. The estimated potential 1-year savings range from a low of about $5.2 billion to a high of nearly $6.7 billion. The lower figure suggests an annual potential rate of return of $6.50 for every dollar invested; the higher figure carries an even more impressive $8.80 for the same dollar. These returns on investment continue for each year the health care advance remains in place.

Next Steps

NIH will continue to assess the economic impacts and yields of biomedical research through identifying and analyzing health care cost reductions made possible by NIH support of applied research and clinical trials.

Care and Use of Animals in Research

Issue

What should NIH do to educate the public and Congress about the importance of using animal models in biomedical research and testing?

Background

During the past two decades, well-organized and vocal opposition to the use of animals in biomedical research and testing has grown stronger. Leaders of the animal rights movement have pressured Congress and the executive branch to impose severe restrictions that could hamper, and ultimately destroy, the NIH effort to maintain and improve the health of the American people.

Current Status

NIH has assumed a pivotal role in promoting the importance of animal research and testing and has identified areas that require an overall strategy or plan of action.

Legislation. Federal legislation introduced during the 98th through the 101st Congresses has been concerned primarily with finding methods that would eliminate or reduce the use of animals in biomedical research and testing and ensure their proper care and humane treatment.

Animal Welfare Act. The 1985 amendments to the Animal Welfare Act directed the U.S. Department of Agriculture (USDA) to promulgate additional regulations governing the care and use of animals in biomedical research; parts 1 and 2 of the regulations became effective in October 1989. NIH and the Office for Protection from Research Risks will continue working with USDA to harmonize the regulations for part 3 (covering humane treatment, handling, and care of research animals) with Public Health Service (PHS) policy.

Silver Spring Monkeys. Three surgically operated monkeys and one control animal remain at the Delta Regional Primate Research Center (Louisiana), and four rehabilitated animals are being maintained at the San Diego Zoo. Neuroscientists want to study the remaining operated animals when each animal's condition deteriorates to the point that veterinarians recommend euthanasia for humane reasons.

Animal Facility Improvements. NIH has continued its efforts to upgrade its intramural animal holding areas to meet the recommendations of the Guide to the Care and Use of Laboratory Animals. Before seeking American Association for Accreditation of Laboratory Animal Care (AAALAC) approval, these facilities will be upgraded at an estimated cost of $22 million. Also, the National Center for Research Resources at NIH will provide

$11 million to NIH grantees to improve 36 extramural animal facilities.

Primate Conservation. NIH will expand its charge to conduct oversight review of all research involving chimpanzees. The national breeding program is currently producing enough animals to meet the needs of the most essential studies.

Adjuncts to Animal Models. In collaboration with private-sector organizations, NIH will prepare a publication for wide public distribution to explain why nonanimal methods cannot substitute for using vertebrate animals in research at this time.

Next Steps

The NIH Action Plan continues to implement many of the animal welfare activities originally planned in 1989. The NIH has established an office of animal research in the Office of the Director, NIH, to coordinate and implement PHS-wide activities aimed at educating the public, Congress, the research community, and health professionals on the need to use animals in biomedical research and testing.

Activities To Improve Grant and Contract Accountability and Peer Review

Introduction

In fulfilling its mission "to improve the health of the people of the United States" through biomedical research and training, NIH makes about 30,000 extramural awards annually to more than 1,600 institutions in every State of the Union and in foreign countries. The impact and value of biomedical research depend heavily on ensuring that the research is carried out and managed in accord with the highest standards of integrity. Thus, major NIH priorities include promoting the responsible conduct of biomedical research and avoiding financial conflicts of interest in awarding and administering public funds for biomedical research.

NIH uses three major extramural award instruments: grants, cooperative agreements, and contracts. Grants and cooperative agreements (assistance awards) for health-related research and research training constitute the largest category of NIH funding. Assistance awards include research and program projects, centers, resources, conferences, and special initiatives (e.g., Small Business Innovation Research and Academic Research Enhancement Award programs). Assistance awards are made after two sequential levels of peer review, both required by law.

NIH research and development (R&D) contracts (acquisition awards) seek solutions to specific requirements to extend and advance biomedical knowledge and technology. R&D contracts typically fund complex clinical trials and development of new therapeutic or preventive drugs, vaccines, and devices. The evaluation principles for competitive R&D contract projects are similar to grant evaluation principles, but the procedures are different. Concepts of proposed projects are reviewed by scientific peer advisory groups, and subsequent proposals receive peer group technical evaluation against criteria specified in a solicitation document (request for proposal).

Improvements in Grant Accountability

In October 1988 the Federal Demonstration Project (FDP) became a cooperative effort among 50 institutions and 9 Federal research agencies. The purpose of FDP is to increase research productivity by streamlining and standardizing administrative procedures and controls. The Deputy Director, NIH, chairs the Interagency Assessment Committee, and Office of Extramural Research (OER) staff serve on a number of FDP committees and task groups.

OER issued a comprehensive policy on implementation of cooperative agreements awards. The policy covers procedures from program advisory recommendations through solicitation and application reviews, to funding and administration of awards, and includes specific OER oversight approval steps for cooperative agreement uses and terms and conditions.

Consistent with applicable laws and regulations, OER implemented new policy guidance for managing NIH peer review appeals and grant appeals for assistance applications and awards.

OER took the initiative to refine the Instructor's Handbook for Public Health Service (PHS) Research Grant Program Officials to better meet the needs of NIH and the Alcohol, Drug Abuse, and Mental Health Administration (ADAMHA). Working with the Project Officers/Program Officials Forum, OER edited the handbook to incorporate special NIH-ADAMHA program and review requirements.

OER and officials of the Department of Veterans Affairs (VA) and university representatives collaborated to clarify conditions under which VA employees may apply for NIH grants and contracts. The policy reaffirms practices permitting VA investigators to conduct research through affiliated universities, and clarifies how applicants may assure peer reviewers and NIH staff that efforts proposed for particular projects are consistent with investigators' total professional commitments.

Improvements in Contract Accountability

The Procurement Integrity Act (PIA), which was implemented at NIH effective July 16, 1989, broadened the categories of NIH officials subject to various restrictions, prohibitions, and penalties. Although the PIA was suspended for 1 year on December 1, considerable training had been provided to NIH staff during the 4 1/2 months the law was in effect. The training served to make both scientific and administrative personnel more sensitive to the need to recognize and avoid conflicts of interest in the acquisition process. If the PIA is reinstated in December 1990, NIH will again provide comprehensive training for scientific and administrative personnel who perform as "procurement officials" under the Act's provisions.

Improvements in Peer Review

OER has implemented policies and procedures for preliminary scientific peer review of grant proposals responding to requests for applications to eliminate those judged noncompetitive for awards. Subsequent indepth scientific evaluations yield definitive recommendations for those competing for funding. These procedures expedite review processes in the face of increased special program initiatives and pace of biomedical research.

OER implemented policies and procedures consistent with requirements of the Procurement Integrity Act (PIA) to ensure appropriate standards of conduct by members of scientific peer review groups who advise NIH components on R&D acquisitions. OER discussed these provisions with procurement and legal officials of the U.S. Department of Health and Human Services and later presented them at an NIH PIA conference on July 13, 1989.

To incorporate recent statute and regulation requirements and help review consultants avoid conflicts of interest more effectively, OER is revising several NIH Manual chapters covering procedures and staff functions in reviews of grant and cooperative agreement applications, and in improved submission of reviewers' financial interest statements.

Improvements in Extramural Programs Management

Conflicts of Interest. NIH acts as the lead PHS agency in coordinating the development of policies and procedures defining the responsibilities of research institutions that receive PHS funds. NIH activities to promote integrity in biomedical research have included continuing education programs and studies to define issues. Important progress in those directions came from the report received under a contract with

the Institute of Medicine that developed principles and procedures to promote scientific responsibility and quality assurance in the health sciences. The report made a number of recommendations to raise the consciousness of scientists and scientific organizations on maintaining responsibility in research.

The PHS Grants Policy Statement outlines the need for awardee institutions to have written policy guidelines on avoiding conflicts of interest. To seek further guidance from institutions regarding conflict-of-interest policies, in 1989 the OER published notices in the *NIH Guide for Grants and Contracts* seeking comments in these areas, and in June 1989 held a 2-day NIH-ADAMHA conference on various conflict-of-interest issues. As a next step toward further guidance to institutions to maintain a healthy research environment, in September NIH and ADAMHA published draft guidelines for institutions. Numerous comments were received. NIH, ADAMHA, and the PHS are working on a follow-up proposal.

Scientific Integrity. Working with the Office of Scientific Integrity, OER has also conducted continuing education programs for NIH-ADAMHA extramural scientific program officials to review issues in ethics, law, and publication practices, and to emphasize responsibilities of the scientific community and NIH extramural staff.

The *NIH Guide for Grants and Contracts* is the main medium by which NIH communicates information to the extramural biomedical community about policies, procedures, and special initiatives. To facilitate dissemination, OER has made the *Guide* available electronically on an experimental basis. More than 100 institutions now receive the *Guide* via BITNET.

Minority Participation. Census Bureau statistics forecast dramatic changes in the composition of the work force beyond the year 2000, with substantial increases in the percentage of minorities. To meet the Nation's biomedical research needs in the face of those changes, OER during this past year developed a series of opportunities for underrepresented minorities to participate in biomedical research and research training opportunities. Supplements of existing grants support various research experiences for high school, college, and graduate students and faculty. In addition, the OER conducted five regional hearings and group discussions to solicit information from the community on how NIH could improve access to increase the participation of underrepresented minorities in NIH-supported biomedical research.

Human Subjects and Animal Welfare Issues. OER officials represented PHS in working with the U.S. Department of Agriculture (USDA) to develop the USDA Animal Welfare Regulations, which were published in the *Federal Register* on August 31, 1989. Incorporation of principles and provisions of existing PHS policy into USDA regulatory format ensured standardization and continuance of accepted grant review requirements.

The primary means of achieving compliance with regulations for protecting human subjects and with policy for humane care and use of laboratory animals is prevention through assurance negotiation and education. Besides negotiating and approving several hundred institutional assurance documents, OER staff presented workshops and seminars to extramural and intramural NIH communities, emphasizing responsibilities and roles of all involved with human or animal welfare issues.

Responding to the NIH Director's recognition of increasing concerns for conservation and care of chimpanzees in biomedical research and to minimize redundancy and the invasiveness of the research, the Deputy Director, OER, charged the Interagency Animal Model Committee to review all NIH-supported research using chimpanzees. Other Federal agencies have agreed to the joint stewardship of these scarce resources.

Biennial Reports of the NIH Institutes, Centers, and Divisions

National Institute on Aging

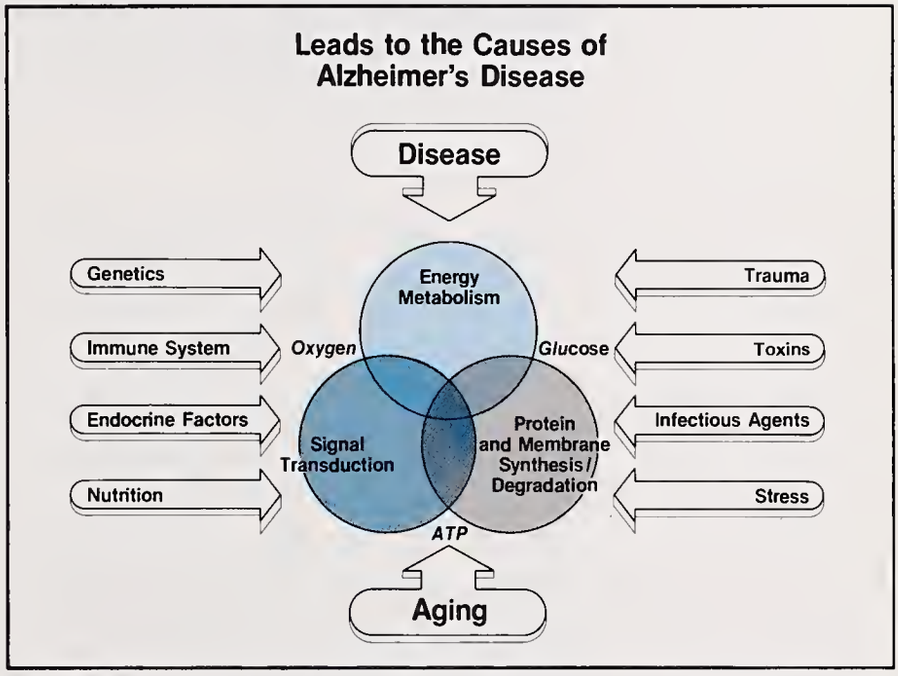
Director's Preface

In its first 15 years, the National Institute on Aging (NIA) has been a principal agent in fostering historic changes taking place in the United States and around the world in gerontology and geriatrics. The resulting NIA research programs encourage opportunities for sustained activity and functioning in old age. The programs also concentrate on alleviating problems that contribute to widespread suffering in older people and the staggering growth of health care costs. Research priorities include Alzheimer's disease (AD); osteoporosis; cardiovascular disease; incontinence; disability from frailty, falls, and injuries; and sensory impairments. The needs of older minority populations, those in rural settings, and the oldest old receive special attention. Companion initiatives foster health-promoting behavior and enhanced geriatric care and rehabilitation.

Alzheimer's Disease

A health crisis of epidemic proportions affecting as many as 4 million older citizens, AD devastates individuals and families and is estimated to cost $80 billion or more per year. The conquest of AD remains NIA's first priority.

Etiology and Diagnosis. Research to discover the cause or causes of AD focuses on establishing genetic linkages and understanding the role of toxins, infectious agents, metabolism, and other factors in producing nerve cell dysfunction and death. A 20-center consortium is improving our understanding of AD as well as the standards and reliability of Alzheimer's diagnosis nationwide. An abnormal protein found in the brains of AD patients was recently discovered in the skin; this finding may lead to developing a single, objective diagnostic test for AD.



One of NIA's highest priorities is to find the cause or causes of Alzheimer's disease (AD). This figure summarizes various factors being studied to determine causes of nerve cell dysfunction and death in AD.

Treatment. Drug compounds currently being evaluated in clinical trials may help control memory loss in some AD patients. Nerve growth factor, which has been shown in rodents to stimulate nerve growth and aid the survival of certain injured brain cells, will soon be tested in nonhuman primates and, once safety and technical questions are answered, in patients with AD and other degenerative nerve diseases. Social and behavioral interventions are being sought to lighten

the burdens for the caregivers of AD patients.

Special Initiatives. Distinguished recipients of Leadership and Excellence in Alzheimer's Disease awards make exceptional contributions to AD research and training. Alzheimer's disease research centers stimulate research collaboration and training, develop educational materials for national distribution, and assist in the establishment of diagnostic and treatment centers to improve AD patient care. A partner in this general effort, the national Alzheimer's Disease Education and Referral Center, established in 1990, gathers information on AD and disseminates it to health professionals, patients, caregivers, and the public.

Understanding Aging and Promoting Health

Cellular and Molecular Mechanisms of Aging and Cancer. Scientists have found striking changes in gene expression in senescent cells versus actively growing cells. For example, NIA intramural scientists studying these changes recently found a new antiproliferative gene. Because aging is accompanied by loss of cell replicative potential, mechanisms regulating cell senescence may eventually be influenced to regulate the uncontrolled proliferation of cancer cells. Investigators are also searching for "longevity assurance genes" in invertebrates and mammals, which may be involved in extended lifespan and healthspan in these species. These and related studies have major implications for both aging and age-related disease.

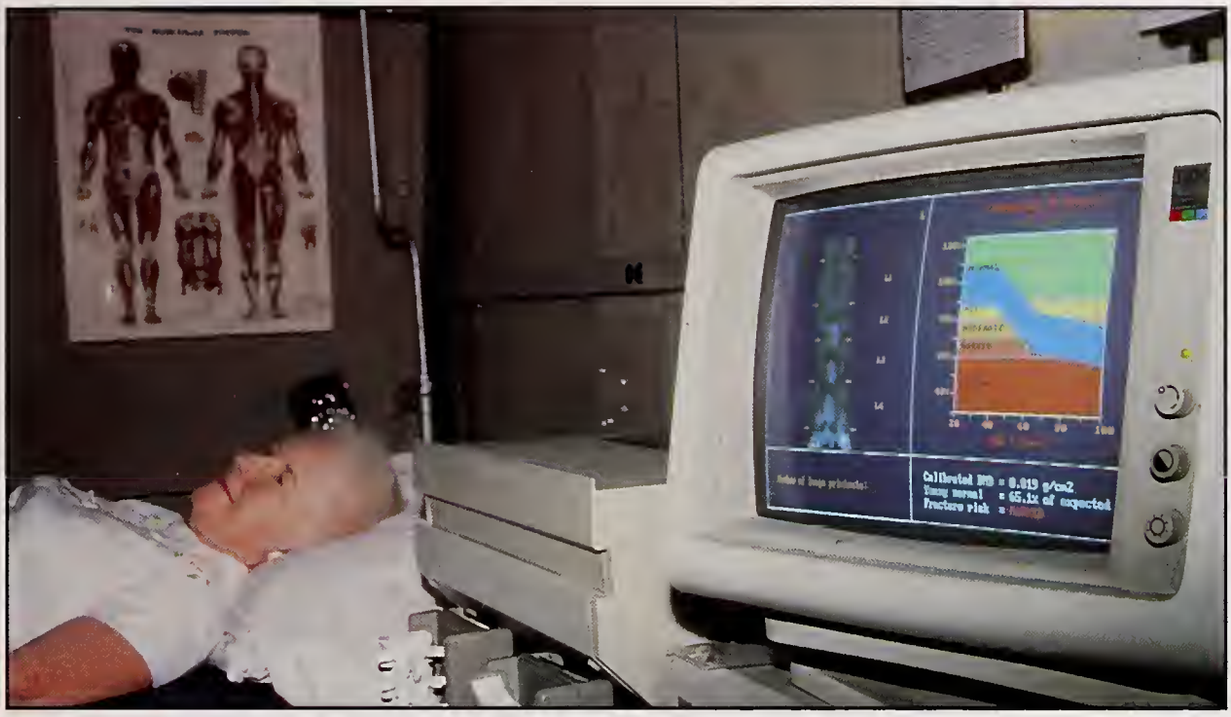
NIA has encouraged initiatives to determine the mechanisms by which lower consumption of calories dramatically lengthens lifespan and prevents age-related diseases, such as cancer, in experimental animals.

Biomarkers of Aging. A major initiative aims to discover biomarkers of aging (physiological, biochemical, and behavioral measurements such as bone metabolism or neuron sensitivity) that can be used to track the rate of aging and the impact of clinical interventions.

Immune Function, Aging, and AIDS. Older persons are more vulnerable to disease because of age-related decrements in immune function. The most significant aspect of immunosenescence, a decrease in cell-mediated (T cell-controlled) immunity, also characterizes human immunodeficiency virus infection. A number of immunologists are pursuing leads toward understanding and slowing this age-related decline in conjunction with NIA research on acquired immunodeficiency syndrome.

Epidemiology and Demography. NIA data collection research has yielded information essential for health care policy-making. Key to this progress has been the Established Populations for Epidemiologic Studies of the Elderly (EPESE), an intramural study in four community-based populations begun in the early 1980's. These and other longitudinal studies indicate that lifestyle factors, including appropriate nutrition, exercise, and smoking cessation, are related to health and well-being in aging. For example, a recent study showed that improving physical fitness, even to only moderate levels, is associated with a longer and healthier life for all age groups. In addition, the National Long-Term Care Survey and the Longitudinal Study of Aging (two NIA-supported data bases) have provided valuable data on disability in the aged, especially in individuals over age 85.

Baltimore Longitudinal Study of Aging (BLSA). The BLSA, conducted at NIA's Gerontology Research Center, has characterized aging in normal volunteers since 1958. The 1,100 active participants are divided nearly equally between men and women and range in age from 19 to 97. A proposed new initiative would broaden the study to include specific populations with age-related diseases.



A volunteer is undergoing a bone scan as part of the Baltimore Longitudinal Study of Aging. The NIA supports a major program of osteoporosis research and prevention.

Productivity, Work, and Retirement. Productivity in the later years improves the health and functioning of older people and can help alleviate America's growing worker shortage. A major NIA effort, including a longitudinal survey, is therefore designed to study unprecedented trends in work and retirement and the interactions of these factors with health.

Reducing Frailty and Dependence

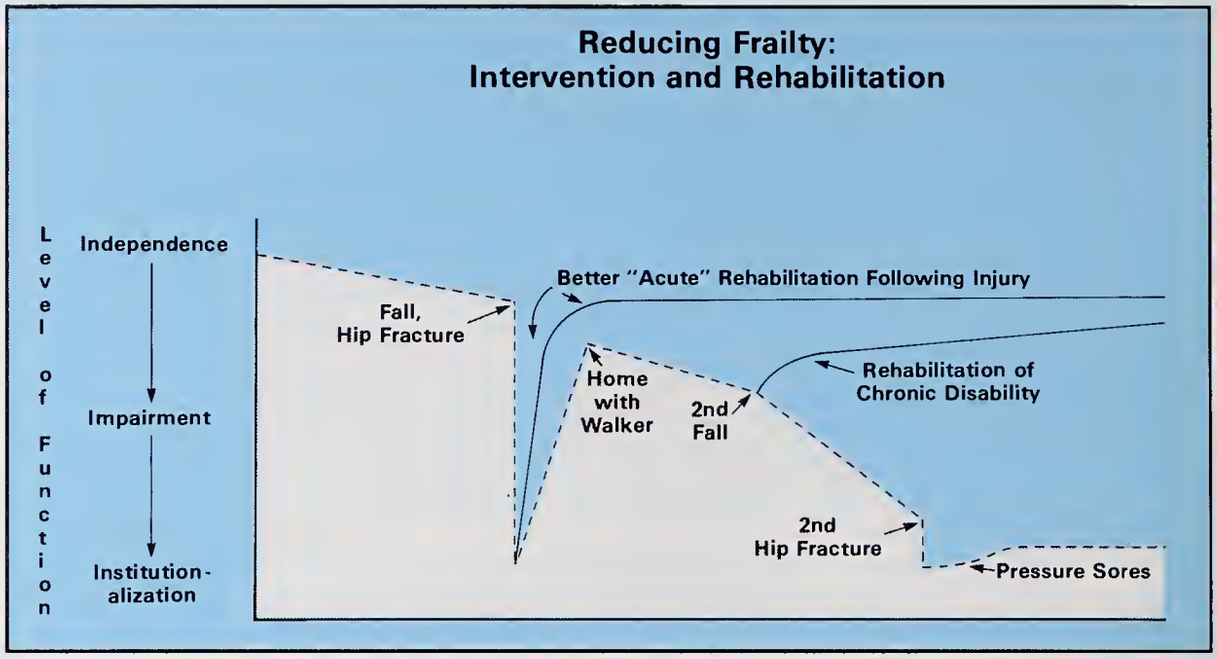
NIA supports a major, long-term initiative on frailty. This condition of severely impaired strength, mobility, balance, and endurance contributes to falls and disabling injuries, such as hip fractures, which cost an estimated $7 billion annually.

Frailty Clinical Trials. In 1990, NIA and the National Center for Nursing Research inaugurated trials to test the effectiveness of biological, behavioral, and environmental interventions to reduce frailty, falls, and fractures. These interventions include exercise and improved nutrition, rehabilitative strategies, and human factors research.

Osteoporosis and Other Musculoskeletal Conditions. Fractures often result from bone loss caused by osteoporosis. The Institute has established a major osteoporosis program focused particularly on preventing hip fractures. NIA is also pursuing promising opportunities for progress against osteoarthritis, degenerative muscle conditions, and age-related disorders of gait and balance.

Urinary Incontinence. Afflicting at least 5 million Americans at a cost exceeding $10 billion per year, urinary incontinence is a serious cause of disability and need for long-term care. In recent clinical studies of this disorder, exercise reinforced with biofeedback produced significant reduction of symptoms.

Geriatric Rehabilitation. Improved geriatric rehabilitative techniques could restore millions of frail older persons to greater independence. NIA's goal is therefore to develop biomedical and psychosocial strategies for rehabilitation of older patients with debilitating illnesses, including victims of stroke and cardiovascular disease, and persons with sensory and cognitive impairments.



Most deficits thought of as inevitable consequences of aging can be ameliorated or delayed through health maintenance and rehabilitation. This figure contrasts the potential benefits of frailty intervention with the physical decline suffered by a 78-year-old woman who did not receive optimal intervention.

Geriatric Pharmacology. Drug misuse and mismedication among older people is a large and growing problem that contributes to frailty and dependency. NIA has solicited proposals on drug metabolism and interaction; adverse drug reactions; dosages; and prescribing patterns, use, and efficacy of medications in older people to provide solutions to this problem.

Human Factors Research. Everyday activities like shopping or bathing can present insurmountable obstacles to older people. Even small changes in the design of a product, task, or environment can extend working life and independent living. NIA is identifying opportunities for studies of such changes in transportation, the workplace, housing, and other environments.

Long-Term Care. Progress in the foregoing areas, including health promotion, would lead to major reductions in long-term care needs and costs. Research is planned on the quality and effectiveness of long-term care, including programs to support families as the primary caregivers and to assess innovative community and institutional services, such as respite and in-home health care, as alternatives to institutionalization.

Cardiovascular Research. NIA and the National Heart, Lung, and Blood Institute are cosponsoring a large clinical trial on treatment of systolic hypertension in older people. NIA intramural laboratories are conducting pioneering research on the aging heart, vascular disease, and methods for predicting future heart disease. Such studies are expected to contribute to a reduction in cardiovascular morbidity and mortality in the aged.

Sleep Disorders. Common among older people, sleep disturbances contribute to abuse of medication and excess mortality. In 1990, NIA sponsored a consensus conference on sleep disorders and helped establish the National Commission on Sleep Disorders Research. NIA aims to discover the causes of these disorders in the aged and to develop better strategies for treatment.

Hearing Loss and Visual Impairment. Sensory disorders jeopardize the autonomy and well-being of large numbers of

older people. NIA studies are defining underlying changes in the nervous system, improving assessment, and designing better prostheses.

Special Older Populations

Minority Aging. NIA has worked aggressively to enhance its existing clinical and cross-cultural investigations with additional studies of minority health status, family life, work and retirement patterns, health-related behaviors, and health care utilization. The Institute has issued solicitations to foster this research, including a minority frailty initiative, as well as to increase the number of minority investigators.

Rural Aging. The EPESE data in Iowa and North Carolina have provided insight into living conditions in rural populations. To augment such data, NIA initiated a centers program in 1990 to study the health, health accessibility and care practices, and quality of life of older rural populations.

Oldest Old. NIA has consistently focused its attention on persons over age 85, the fastest growing segment of the U.S. population and the group at greatest risk for disease and disability.

Training for New Investigators

Only a small fraction of the number of clinical investigators needed to lead geriatric medicine and train future geriatric scientists has been developed. To help alleviate this shortage, NIA established the Claude D. Pepper Geriatric Research and Training Centers Program. Two other new NIA award programs designed to use the resources of these centers provide geriatricians with the research skills needed for academic leadership.

This recipient of a Minority Access to Research Careers award received training at the Nathan W. Shock Gerontology Research Center. The NIA is committed to expanding research on minority aging and developing minority investigators.

Conclusion

NIA's first 15 years have produced a comprehensive research effort designed to understand the nature of aging and its health and societal implications. At the broadest level, this effort is concerned with the fundamental processes of aging and what old age can become through the elimination of disease and disability. At a more immediate level, the research is making available practical, effective interventions for older people and their families. These efforts are contributing to a society prepared to enjoy the gift of a healthy and satisfying old age.

National Institute of Allergy and Infectious Diseases

Director's Preface

This decade is an era of great biomedical accomplishments and unprecedented emerging research opportunities, which are made possible largely by advances in immunology and microbiology. Many of those advances are the fruit of basic research supported by the National Institute of Allergy and Infectious Diseases (NIAID). Over the past decade, NIAID researchers dedicated to unlocking the fundamental mystery of how the human body protects itself from disease have expanded this knowledge by pioneering sophisticated medical technologies. Millions of people today are reaping the benefits of NIAID's past investments in basic research. NIAID's current basic research programs continue to be a vital investment in tomorrow's achievements and will lay the foundation not only for treating and preventing many devastating or unforeseen diseases but also for eradicating them as well.

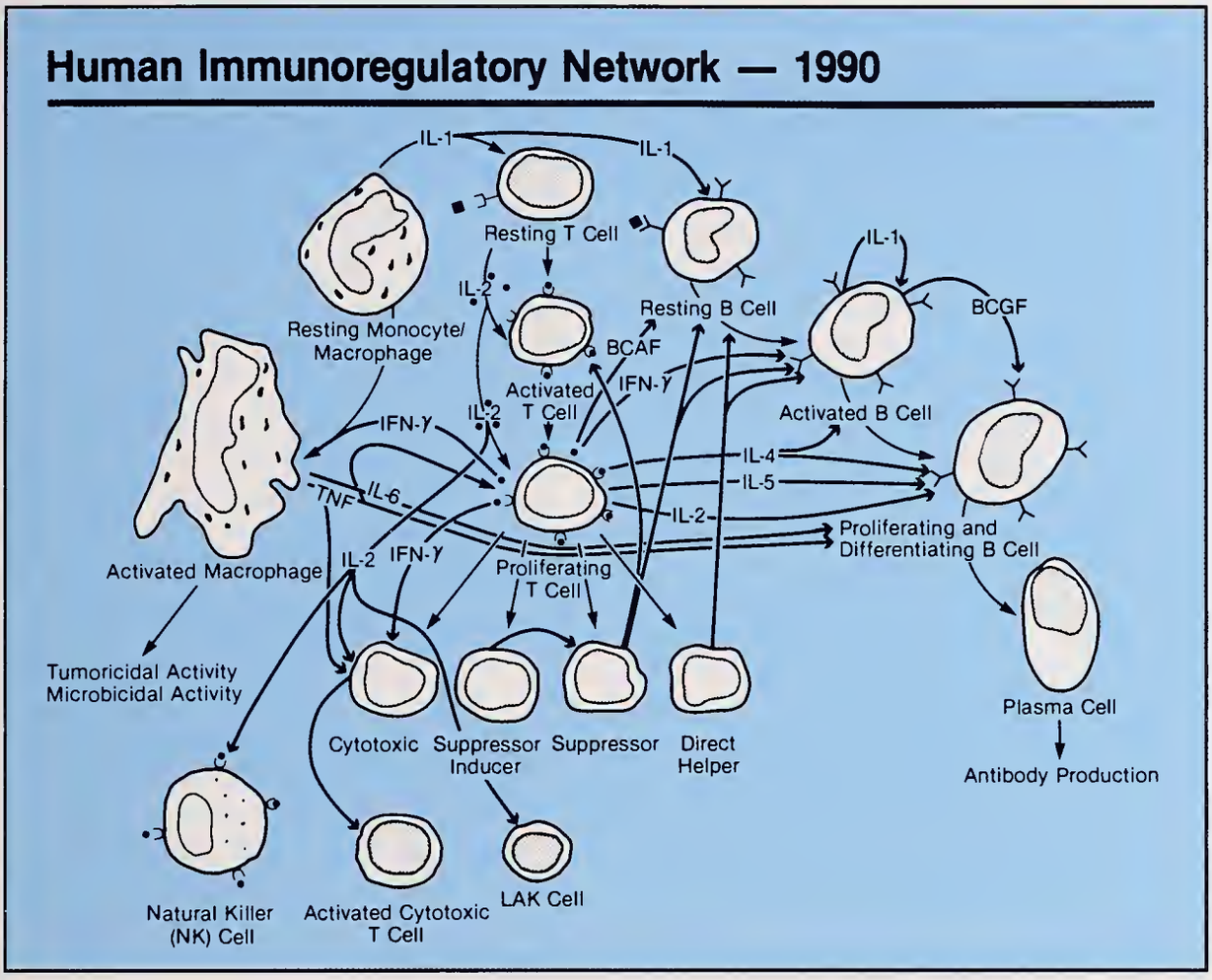
Expanding Essential Knowledge

Basic Immunology, Allergy, and Transplantation

A primary NIAID goal is to understand the intricacies of the immune system—unraveling its biological, chemical, and genetic nature and understanding the disease response at the cellular and molecular levels.

Cytokines are a significant focus of NIAID's basic research in immunology. These powerful protein mediators of the immune system promise to improve transplant outcomes; control allergic, asthmatic, and inflammatory diseases; and augment cancer chemotherapy. For example, NIAID grantees recently produced a molecule linking diphtheria toxin to interleukin-2, a special type of cytokine that acts like a "magic bullet," specifically binding to and eliminating cells responsible for transplant rejection. NIAID scientists are also exploring interferon-gamma (another cytokine), which shows dramatic promise in protecting people with recurrent life-threatening infections and which has the potential to treat other severely immunocompromised individuals including the elderly and cancer patients. Finally, NIAID-supported scientists have also suppressed the action of interleukin-4, a potent chemical in allergic and hypersensitivity reactions. This advance opens new and more effective ways to control allergic conditions that affect nearly 20 percent of the U.S. population.

As essential knowledge of immunology grows, NIAID's research will play a critical role in solving numerous health problems, especially conditions leading to transplantation, asthma, and diabetes. Because these conditions disproportionately afflict children, minorities, and inner-city populations, NIAID's expanding leadership in understanding and



In 1968, knowledge of the human immune system was limited primarily to the functions of the B and T cells. During the past 20 years, however, NIAID-sponsored research has dramatically increased knowledge of the immune system, which is essential to understanding the disease process.

treating these conditions is essential to improving public health.

Microbiology and Infectious Diseases

Finding the biomedical means to control diseases caused by infectious agents is vital to NIAID's mission. Doing so involves a wide range of research—from microbial studies that examine viral, bacterial, fungal, and parasitic mechanisms of infection and pathogenicity, to vaccine trials and epidemiological studies.

Hepatitis C. A new technique to detect the hepatitis C virus (previously known as non-A, non-B hepatitis) exemplifies how scientists rely on NIAID's past research in infectious diseases to promote public health. In 1989, investigators detected the hepatitis C virus in blood from infected individuals by using a procedure derived from the basic research of NIAID intramural scientists. This discovery was the first step in developing a hepatitis C screening test for blood donors, the ultimate goal of which is to help prevent transmission of the virus that causes chronic hepatitis, cirrhosis, and chronic liver failure (one of the 10 leading causes of death in the United States).

Antiviral Drugs. Antiviral drugs are becoming key weapons in the battle against human viral infections, ranging

from the common cold to lethal diseases. This struggle is complicated because viral replication occurs inside cells, subverting normal cellular functions. To identify compounds that selectively inhibit viral replication without irreparably damaging the host, NIAID's antiviral screening facilities are evaluating 60 promising compounds, including drugs with selective activity against the herpes virus, respiratory syncytial virus, influenza virus, and parainfluenza virus.

Vaccines. The biotechnology revolution has enhanced NIAID's capacity to accelerate the development of new vaccines, one of the most cost-effective ways to prevent serious and sometimes fatal illness. Some of NIAID's most promising and exciting vaccines will greatly reduce morbidity and mortality, particularly among infants and children. Included are a vaccine for *Haemophilus influenzae* type b, which causes bacterial meningitis, and a vaccine for group B streptococcus, which causes death or permanent disability in half the infants infected. In addition, physicians, public health officials, and parents await the outcome of NIAID comparative trials to find a new, safer, and more effective vaccine for pertussis.

Sexually Transmitted Diseases (STD's) and Tuberculosis (TB). Progress against two other serious health problems, STD's and TB, continues through NIAID's research in microbiology and infectious diseases. STD's, many of which are implicated as cofactors in transmitting the human immunodeficiency virus (HIV), compromise the health of women and children by causing infertility, ectopic pregnancy, cervical cancer, fetal wastage, premature births, and congenital infection. NIAID-supported researchers are working toward new vaccines and treatments for a wide range of STD's including gonorrhea, chlamydia, syphilis, genital herpes, human papillomavirus infection, and pelvic inflammatory disease. NIAID is also supporting the development and distribution of more effective and less costly means to diagnose STD's to meet the urgent needs of clinics serving a growing population of infected individuals in American inner cities and in developing countries.

After a nearly 40-year decrease in U.S. incidence rates, growing concerns about TB are emerging as the number of cases no longer declines. TB also poses an increasing threat, especially to minority populations in this country and continues to be a major international health problem accounting for approximately 10 percent of the world's deaths. To meet this challenge, NIAID-supported researchers are attempting to engineer a better vaccine, develop new diagnostic reagents, and evaluate aconiazid, a new, less toxic drug treatment.

Acquired Immunodeficiency Syndrome (AIDS)

Nowhere is there a better example of how basic research can yield incalculable dividends than in AIDS research. Extraordinary advances have not only extended the lives of many HIV-infected individuals but have also created promising avenues for antiviral research, potential cures for STD's, and therapeutic agents for many opportunistic infections that take the lives of immunosuppressed cancer patients and organ transplant recipients.

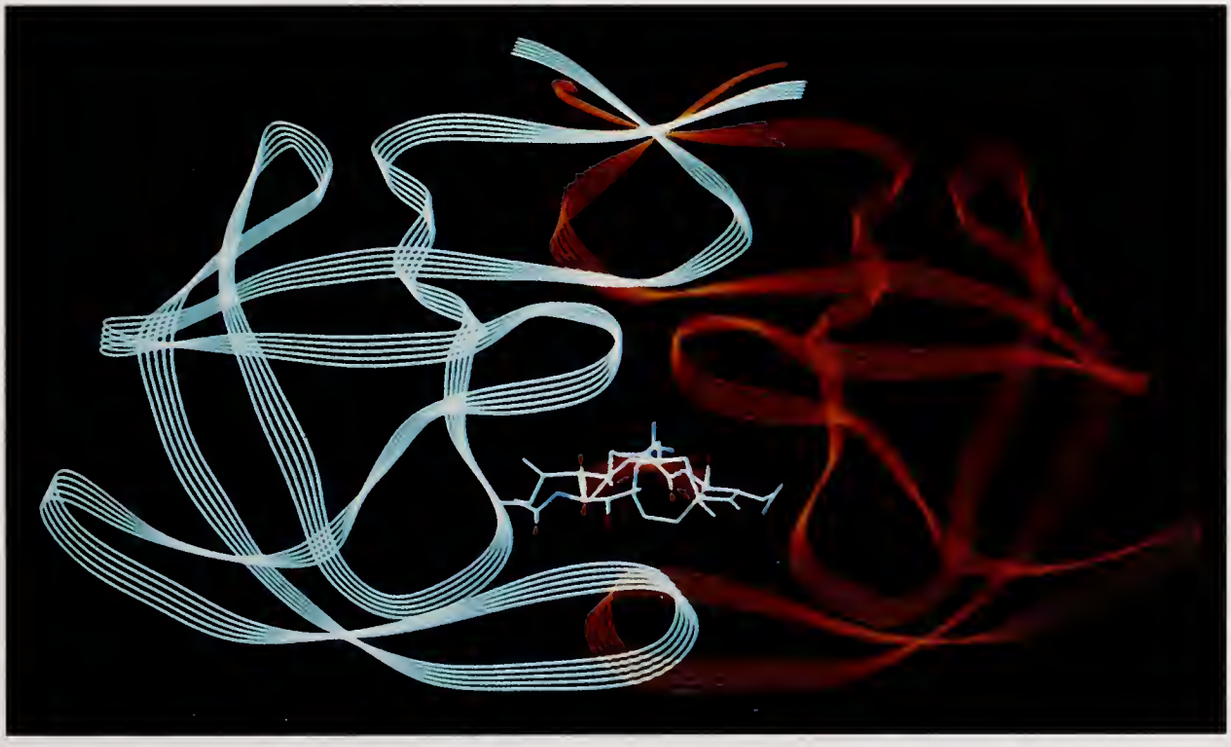
Zidovudine (AZT). NIAID-supported studies concerning AZT (an antiviral drug approved in 1987 to treat persons with AIDS) have demonstrated that it can delay disease progression in HIV-infected persons who have no symptoms, or early symptoms, of disease. The studies also show that AZT can be effective and less toxic at half the dose originally recommended. The implications of this research are that a growing number of HIV-infected individuals can benefit from early, less toxic drug treatment and that striking changes in treatment regimens will ultimately affect the range, frequency,

intensity, and cost of AIDS-related health care.

Vaccine and Drug Development. NIAID supports drug development in the quest for safer, less expensive, and more effective AIDS therapies. For example, scientists have explored the HIV protease (an enzyme used to replicate the AIDS virus) and have unveiled the structure of MTV-101 (a compound that binds to the HIV protease and inhibits its activities). Knowing the crystalline structure of the protease, researchers can identify potential molecular targets and design more potent, specific AIDS therapies. Meanwhile, at least 35 additional drugs or combinations of drugs are being investigated by scientists at the 47 units that comprise the AIDS Clinical Trials Group; 15 of these units conduct clinical trials in children exclusively, and 7 of the adult units also perform pediatric studies. The first of these studies has already established that AZT can prolong survival and relieve severe AIDS symptoms in children under age 13.

One exciting NIAID-supported advance comes from research demonstrating that a human AIDS vaccine is possible. In these studies, when a prototype AIDS vaccine made from a virus that infects rhesus monkeys was injected into the animals, the vaccine protected them from infection. Researchers believe that the monkey model will enable them to identify the specific immune responses that protected the animals against infection and will eventually lead to a human vaccine.

Finally, NIAID has funded 18 Community Programs for Clinical Research on AIDS (CPCRA) to reach out to HIV-infected blacks, Hispanic-Americans, intravenous drug users, and women, and to get community-based physicians who work on the front lines of the AIDS epidemic involved in clinical research. To provide ready information about NIH- and industry-sponsored trials and related drug therapies, NIAID has also established the AIDS Clinical Trials Information Service, a toll-free, bilingual telephone line.



A computer-generated illustration of the structure of an HIV protease inhibitor complex, which is the target of potent new drugs to inhibit HIV replication, as determined by x-ray crystallography.

Biotechnology Advances

NIAID-supported research has pioneered or advanced several important biotechnologies, including polymerase chain reaction (PCR), monoclonal antibodies, and specific animal models.

Polymerase Chain Reaction. From an impressive array of new biotechnologies, PCR is one of the most notable because of its power, versatility, and potential uses. This procedure, which enables researchers to multiply and probe for minute quantities of genetic information, is used by scientists to observe otherwise undetectable pathogens and to study incomplete genetic material involved in the disease process. Most recently, NIAID researchers used PCR to detect very early HIV infection and to develop an accurate, rapid diagnostic test for the elusive bacterium that causes Lyme disease. PCR has also accelerated NIAID research in STD's, and it promises to enlarge the number of persons who benefit from lifesaving transplantation procedures through improved donor-recipient matching techniques.

Monoclonal Antibodies. Monoclonal antibodies were first developed nearly two decades ago. Innovative applications of these reagents in immunology and microbiology now allow many diseases to be prevented, diagnosed, and treated. Monoclonal antibodies have been used to develop new, improved vaccines for *Haemophilus influenzae* type b, pertussis, and other conditions; new research has shown that these reagents can help deplete or cleanse the bone marrow of potentially dangerous T cells. This procedure may allow bone marrow transplant patients to avoid the often fatal condition of graft-versus-host disease.

Severe Combined Immunodeficient (SCID) Mouse and Other Animal Models. To study the human immune system, understand viral pathogenesis, and test potential antiviral agents and vaccines, NIAID supports the development of smaller, less costly, and increasingly manageable animal model systems. Among the most exciting models developed by NIAID-supported scientists is the SCID mouse. These mice, which lack an immune system, can be implanted with human immune cells and then infected with HIV to study the natural progression of the illness and to evaluate potential drugs or vaccines. Other strains of mice are being developed to study genetics, organ transplantation, and other disorders, including multiple sclerosis and arthritic conditions.

Future Opportunities

NIAID's investment in basic research in immunology continues to produce extraordinary dividends because it is so central to treating and curing countless diseases. To continue creating future opportunities, NIAID is investing in emerging technologies including microencapsulation, which may help develop a whole new class of lifesaving vaccines for many enteric, respiratory, parasitic, and sexually transmitted diseases, and gene transfer technology, which promises potential cures for certain immunodeficiency diseases and has multiple uses in transplantation biology and controlling viral diseases.

In terms of resource challenges, NIAID is working to overcome the pressing, growing problem of attracting and retaining highly trained scientists. Without a broad complement of researchers, the Nation and NIAID will be unable to confront future epidemics of infectious and deadly diseases. However, by applying the knowledge gained over the past several decades and by reinvesting in basic and developmental research as well as in training, NIAID will continue its leadership role in unraveling the disease process and reducing its toll on human lives.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Director's Preface

Established in April 1986, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) has a mandate that embraces a large number of diverse diseases, most of which are long-term and disabling and affect millions of Americans. Since the Institute was established, significant strides have been made in expanding the scope of both its extramural and its intramural programs.

NIAMS conducts and supports both basic and clinical research, including epidemiologic studies and clinical trials, on the many forms of arthritis and diseases of the musculoskeletal system and the skin, as well as on the normal structure and function of joints, muscles, bones, and skin. Basic research involves a wide variety of scientific disciplines, including immunology, molecular biology, genetics, biochemistry, physiology, virology, and pharmacology. Clinical research addresses the fields of rheumatology, orthopedics, bone endocrinology, sports medicine, and dermatology.

The Institute extramural program conducts this research through investigator-initiated research grants, program projects, centers grants, cooperative agreements, interagency agreements, and research contracts. In addition, the Institute funds both research career manpower development and research training awards. Epidemiology studies are undertaken in collaboration with the Centers for Disease Control, the Indian Health Service, the World Health Organization, and through the U.S.-U.S.S.R. Cooperative Program in Arthritis and Musculoskeletal Diseases, as well as the U.S.-Italy Science and Technology Bilateral Agreement.

NIAMS conducts an active, growing intramural research program in its own laboratories and clinical facilities; the intramural program has made significant progress this year. The Orthopedic Research Unit was established in 1988; the Laboratory of Skin Biology and Laboratory of Structural Biology Research were inaugurated early in 1990.

Research Program

Research Progress and Accomplishments

Arthritis and Other Rheumatic Diseases

Rheumatic diseases afflict more than 37 million Americans and cause an annual loss of billions of dollars to the Nation's economy. These costs do not even begin to reflect the emotional and physical tolls paid by people who have one of the more than 100 rheumatic diseases. In recent years, significant research progress has been translated into better patient care.

Systemic Lupus Erythematosus (SLE). SLE is an inflammatory, immune-mediated disorder that causes distinctive rashes, arthritis, and kidney damage. Institute scientists have recently completed a

20-year followup study of patients with lupus nephritis, one of the most serious complications of SLE. Data on patients randomized to three different drug treatments indicate that fewer persons developed kidney failure in the group given intravenous cyclophosphamide than in the other two groups.

Rheumatoid Factor. Approximately 2.1 million adults in the United States suffer from rheumatoid arthritis; symptoms include inflammation of joints with acute pain and fatigue. An immunologic hallmark of the disease is production of an abnormal antibody called rheumatoid factor. Recently, NIAMS-supported investigators discovered that the body's production of rheumatoid factor is controlled by cytokines (messenger molecules produced by white blood cells). Other NIAMS investigators have shown antigenic mimicry of rheumatoid factor by a protein of microbial origin. These findings suggest that the immune response to external invasion could induce or modulate rheumatoid factor production.

Lyme Disease. Lyme disease, which is caused by a bacterium carried by ticks, is a growing problem; some 5,000 new cases were reported in the United States in 1988. Using highly specific antibodies, researchers recently developed a test for detecting Lyme disease bacteria in urine. This new test may prove to be faster and more accurate than the diagnostic blood tests in current use.

Receptor for Immunoglobulin E (IgE). NIAMS intramural scientists recently determined the complete structure of a key protein—the IgE receptor—critical in triggering allergic reactions. They then developed a tissue culture system that expresses human IgE receptors. The system is now being used to search for drugs that will prevent allergy attacks. This breakthrough also has important implications for better understanding and controlling inflammation associated with certain rheumatic diseases.

Muscle Biology

Research in this area is aimed at gaining a better understanding of normal muscle development and function as well as of the pathophysiology of muscle diseases. Modern techniques in molecular biology and genetics are providing new insights into genetic muscle diseases and the mechanism of muscle contraction.

Fundamental Defect in Muscular Dystrophy. Duchenne's muscular dystrophy (DMD) is a devastating, ultimately fatal genetic disease occurring once in every 3,500 live male births. Children are born without symptoms but typically develop muscle weakness around age 6, followed by increasing motor difficulty. Intramural scientists recently examined single muscle fibers of patients with DMD and found that the muscle fibers functioned normally, suggesting that the clinical weakness in DMD may be due to a deficiency in the number of muscle fibers rather than to a defect in the fiber itself. Further research, enhanced by the recent cloning of the gene responsible for DMD, could lead to a better understanding of this debilitating disease.

Musculoskeletal Diseases

Millions of people in the United States suffer from bone and joint diseases, fractures, and disorders of tendons and ligaments. The ultimate aim of musculoskeletal research supported by NIAMS is to improve the quality of life by preventing and reducing suffering from health problems such as osteoporosis, heritable connective tissue diseases, and athletic and sports injuries.

Estrogen Receptors in Healing Bone Fractures. A useful rat model for the study of osteoporosis and fracture healing has been developed by NIAMS intramural scientists. Using a relatively new technique—the polymerase chain reaction (PCR)— investigators have shown increased expression of the gene for the estrogen receptor after bone

injury, suggesting a role for estrogen in healing of osteoporosis-related fractures. Current studies are evaluating the effect of estrogen replacement on the rate and strength of repair after fracture.

Fluoride in Treating Osteoporosis. Recently, a major long-term clinical trial to determine if sodium fluoride is effective in treating osteoporosis was completed. Results indicate that sodium fluoride at the dosage level tested does increase bone mass but does not protect from fractures. Accordingly, sodium fluoride therapy for osteoporosis cannot be assumed efficacious at this time.

Greater Bone Density in Active Young Women. In other NIAMS-supported research, investigators have recently shown that women aged 25 to 34 years who are physically active have significantly higher spinal bone mass than women of the same age who are physically inactive and that the mineral content of bone is affected by calcium intake. Regular exercise and adequate calcium intake throughout life may significantly delay the onset of osteoporotic fractures.

Genetic Defects in Osteogenesis Imperfecta (OI). OI is a major heritable disorder of connective tissue characterized by recurring fractures on minimal trauma. One or more defects in the genes that code for collagen are thought to play a critical role in the pathogenesis of OI. Investigators recently used the PCR to characterize a specific DNA defect that alters the assembly of collagen and leads to the bone defects of OI.

Skin Diseases

An estimated 60 million Americans have one or more skin conditions significant enough to be seen at least once by a physician. There are many kinds of skin diseases; most of them cause much physical and psychological suffering. Included are blistering diseases such as epidermolysis bullosa (EB) and pemphigus; keratinizing disorders such as psoriasis and ichthyosis; atopic dermatitis and other chronic inflammatory skin diseases; cutaneous manifestations of connective tissue diseases, such as scleroderma; pigmentation disorders; and disorders of hair, such as alopecia areata.

The Immune System in Psoriasis. Psoriasis is a chronic skin disorder that affects about 3 million people in the United States. The disease varies from mild to severe and is characterized by rapid cell turnover. The underlying

This elderly man on his daily bike ride illustrates all three of the major disease categories that concern the Institute. Bicycling reduces the chronic pain due to arthritis. It also slows the bone loss from osteoporosis that poses the serious problem of bone fractures for older people. Wearing a hat and other protective clothing reduces the amount of skin-damaging ultraviolet radiation that he receives from the sun, and thereby reduces the chances of developing skin cancers.

etiology is unknown. Recently, the immunosuppressant cyclosporine has shown some effectiveness in the treatment of psoriasis, and other research indicates that psoriasis regresses in individuals infected with human immunodeficiency virus who are being treated with zidovudine (AZT). By studying how cyclosporine and AZT work, researchers are coming closer to understanding the cause of psoriasis and its relation to the body's immune system.

Genetic Markers for Severe Blistering Disease. EB is a group of devastating blistering diseases that may affect as many as 50,000 Americans. The National Epidermolysis Bullosa Registry established by NIAMS is functioning both to collect patient data and material and to assist researchers investigating EB. In a recent study, researchers were able to identify human leukocyte antigens (genetic markers) on the cell surfaces of patients with recessive dystrophic EB, one of the most severe forms of the disease. Preliminary findings indicate that there may be a linkage between the specific genetic defect and specific genetic markers.

Genetic Control of Bullous Pemphigoid. Another blistering disease in which progress is being made with the use of molecular genetic techniques is bullous pemphigoid, which affects the elderly and can be life threatening. In recent studies, NIAMS-supported researchers have managed to isolate cDNA segments that code for the bullous pemphigoid antigen. This advance is providing additional information about the immunopathology of the disease.

Future Research Opportunities

Arthritis and Other Rheumatic Diseases

Immunologic Pathways in Systemic Lupus Erythematosus. Recent research has greatly improved immunologic and genetic understanding of SLE. It is now known that the abnormal antibodies produced in SLE have chemical characteristics that enable them to target and injure specific organs such as the kidney. It has also been discovered that the disease is genetically linked. To exploit these and other advances, NIAMS plans to sponsor an international workshop on research directions in SLE in 1991.

Immunogenetic Marking in Juvenile Arthritis. Considerable progress has been made in determining the immunogenetic basis of arthritis in children. Investigators have found that juvenile arthritis is associated with several tissue-type antigens, suggesting a link between juvenile arthritis and genetic factors. If susceptibility to the disease can be identified with a region of a particular gene, new therapeutic interventions may be possible.

Transgenic Model of Spinal Arthritis. In 1989, for the first time, scientists were able to manipulate mice genetically so that they would carry in their blood a tissue type that has long been known to be associated with human arthritis of the spine. The genetically altered mice were found to be more likely to die following bacterial infection than normal mice. These transgenic mice represent a unique opportunity to investigate the roles of both infectious agents and the immune system in the causation of arthritis.

Muscle Biology

Contraction and relaxation of muscle is modulated through release and sequestration of calcium by channels that function in muscle cells. By exploiting recent advances in genetics and genetic engineering, investigators are learning more about the relationship between the structure and the function of these channels and about the protein responsible for transmitting excitatory signals that facilitate uniform contraction and relaxation. In April 1990, the Institute convened a workshop in which leaders in the field of molecular organization of skeletal muscle provided a comprehensive review

of current knowledge and identified future research opportunities.

Musculoskeletal Diseases

Epidemiologic Research on Osteoporosis. NIAMS is collaborating with the World Health Organization and the National Institute on Aging to conduct a major epidemiologic study to determine if rates of osteoporosis and fractures vary among countries. Differences among groups may lead to identification of genetic or environmental risk factors. In line with this goal, some progress has been made in understanding why the prevalence of osteoporosis in black persons is lower than in white persons (the turnover of bone has been found to be less in blacks than in whites). Research has shown that blacks develop a 10-percent higher adult peak bone mass than whites, which provides some protection from osteoporosis. The unraveling of this interesting metabolic phenomenon could lead to additional new approaches to prevent and treat osteoporosis.

Enzymes That Destroy Cartilage. Osteoarthritis, which afflicts 18 million Americans, is a slowly progressive disease characterized by degradation of cartilage, the protective material that covers and cushions the ends of bones. Scientists have purified one of the enzymes that degrade human cartilage. Future research aimed at suppressing this enzyme could reduce or stop the degradation of cartilage matrix.

Skin Diseases

New Animal Model of Epidermolysis Bullosa. Research into the cause, pathogenic mechanisms, and potential treatments for EB has been hampered by lack of an animal model. Recently, however, scientists have discovered an inbred flock of white alpine sheep that manifest all the characteristics of recessive dystrophic EB. This new animal model will serve to further research into potential treatments.

Immune and Biochemical Reactions to Ultraviolet Radiation (UVR). An NIH consensus development conference on sunlight, UVR, and the skin was held in May 1989, sponsored by NIAMS and the Office of Medical Applications of Research and cosponsored by several other NIH institutes and Federal agencies. Among the areas identified for further research were the effects of UVR on the skin and the biology of aging skin. Although some of the adverse effects of UVR are known, the specific mechanisms involved are not well understood. Only recently has it been recognized that UVR modifies immune function both locally and systemically. Research will continue to study the immune dysfunction of skin resulting from both acute and chronic UVR exposure.

Molecular Mechanisms of Wound Healing. Healing of skin wounds from traumatic injury and surgical procedures is of great medical interest; it also has a major impact on health care costs in the United States. During the past several years, knowledge concerning interventions that seem to speed wound healing has been enhanced greatly by the development of several types of "second skin" dressings, which have been shown to be useful in many diverse clinical situations. The basic processes by which they improve wound healing, however, are not well understood. Future research efforts will focus on molecular mechanisms and clinical aspects of wound healing.

National Cancer Institute

Director's Preface

The role of the National Cancer Institute (NCI) is to support a community of scholars working to generate knowledge that can help reduce death and suffering from cancer. While basic research remains NCI's highest priority, the Institute must foster broad application of the results of that research. It is estimated that cancer mortality rates could be halved by using only what is already known about cancer prevention, early diagnosis, and treatment. Continuing the commitment to elucidate the fundamental nature of cancer while promoting lifestyle changes—better diets, smoking cessation, and limited alcohol consumption—and better access to early detection, diagnosis, and treatment form the basis for solving the cancer problem.

Cancer statistics show higher incidence and mortality for many tumors among minorities, people aged 65 and older, rural residents, and the poor and underserved. Addressing these disparities is a major NCI priority. Recruiting minority group members to careers in cancer medicine and cancer research, increasing minority patient enrollment in clinical trials, and stimulating basic and etiologic research on the causes of differential mortality rates have all been emphasized. The NCI-sponsored National Black Leadership Initiative on Cancer enlists business and community leaders across the country to help organize and promote cancer prevention and control programs. NCI is targeting information programs on prevention and screening to special populations, sponsoring research on patterns of care for minorities and people aged 65 and older, and encouraging NCI-supported cancer centers to focus attention on the needs of the communities in which they are located. Through these and other activities, NCI is promoting access for all to the research advances and technologies generated by the National Cancer Program.

Making Medical History

Biological Modifiers. Adoptive immunotherapy fights disease by mobilizing the body's own immune defenses. Tumor-infiltrating lymphocytes (TIL's) are white blood cells that infiltrate solid tumors and mediate destruction of malignant cells. A patient's own TIL's can be isolated from a tumor, expanded 10,000-fold, and returned to the body, where they traffic directly to tumor deposits. About one-half of patients with melanoma show objective responses to this treatment. Specific TIL's have also been grown to treat patients with renal cell carcinoma. In 1989, two NCI scientists and a colleague from the National Heart, Lung, and Blood Institute carried out a historic gene transfer experiment that had received extensive advisory and regulatory review. TIL's containing a foreign gene were transferred into human patients with advanced cancers. The goal of the initial study was to monitor the TIL's, which were expressing the inserted gene, to determine their distribution and survival. Based on this work, researchers are planning future studies using TIL's that have been

genetically modified to improve their antitumor activity.

Progress Toward a Unifying Hypothesis of Cancer Development. Scientists have identified a set of genes that retard the development of cancer, called suppressor genes. Together with oncogenes (the family of genes that accelerate the malignant process), tumor suppressor genes suggest an elegant, unifying hypothesis about the genetic basis of cancer. Recently, alterations or losses of the p53 tumor suppressor gene on chromosome 17 have been described for many kinds of human cancers including colon, lung, brain, and breast. An NCI grantee has shown that the loss of multiple tumor suppressor genes from chromosomes 5, 17, and 18, and activation of the ras oncogene participate in the development of colorectal tumors. This new model substantiates the longstanding hypothesis that cancer develops as a result of a chain of mutational events. In the near future, physicians may use detection of these molecular alterations to diagnose colon cancer at an early stage. The number of mutations may prove to be a prognostic measure of tumor progression or aggressiveness so that the most appropriate therapy may be prescribed. These findings offer new research opportunities to prevent or treat cancer by interfering with the activity of oncogenes or restoring the effects of altered suppressor genes.

Interrupting Progression to Advanced-Stage Cancer. NCI scientists are making progress toward understanding and controlling metastasis (the spread, invasion, and growth of a tumor at a distant site). Tumor metastasis is the major cause of death from the most common types of cancer. This process depends on tumor cell motility and localized breakdown of the protein layers between cells. Normal cells tightly control this breakdown by a variety of mechanisms, including the activity of growth factors and inhibitors. Tumor cells, on the other hand, produce destructive enzymes in an unregulated manner. Investigators have identified and characterized a number of gene products that play a role in this balance between positive and negative regulation. Increased levels of type IV collagenase, an enzyme produced in large amounts by tumor cells, were found to be strongly correlated with the transition from noninvasive to invasive and metastatic bladder, gastric, and colon cancers. This enzyme carries its own inhibitor, the function of which is lost during cancer progression, suggesting new therapeutic strategies for blocking type IV collagenase activity. Autocrine motility factor (AMF) is another metastasis-associated gene product of cancer cells that profoundly stimulates their locomotion. NCI scientists have developed a specific inhibitor of the AMF pathway and of tumor cell motility. The expression of a newly discovered tumor suppressor gene (NM23) was found to be associated with tumors of low metastatic potential and absent in aggressive breast cancers. A panel of prognostic markers that includes these metastasis-associated gene products may soon be used to predict the aggressiveness of a cancer and thus aid clinicians in determining the most appropriate course of treatment.

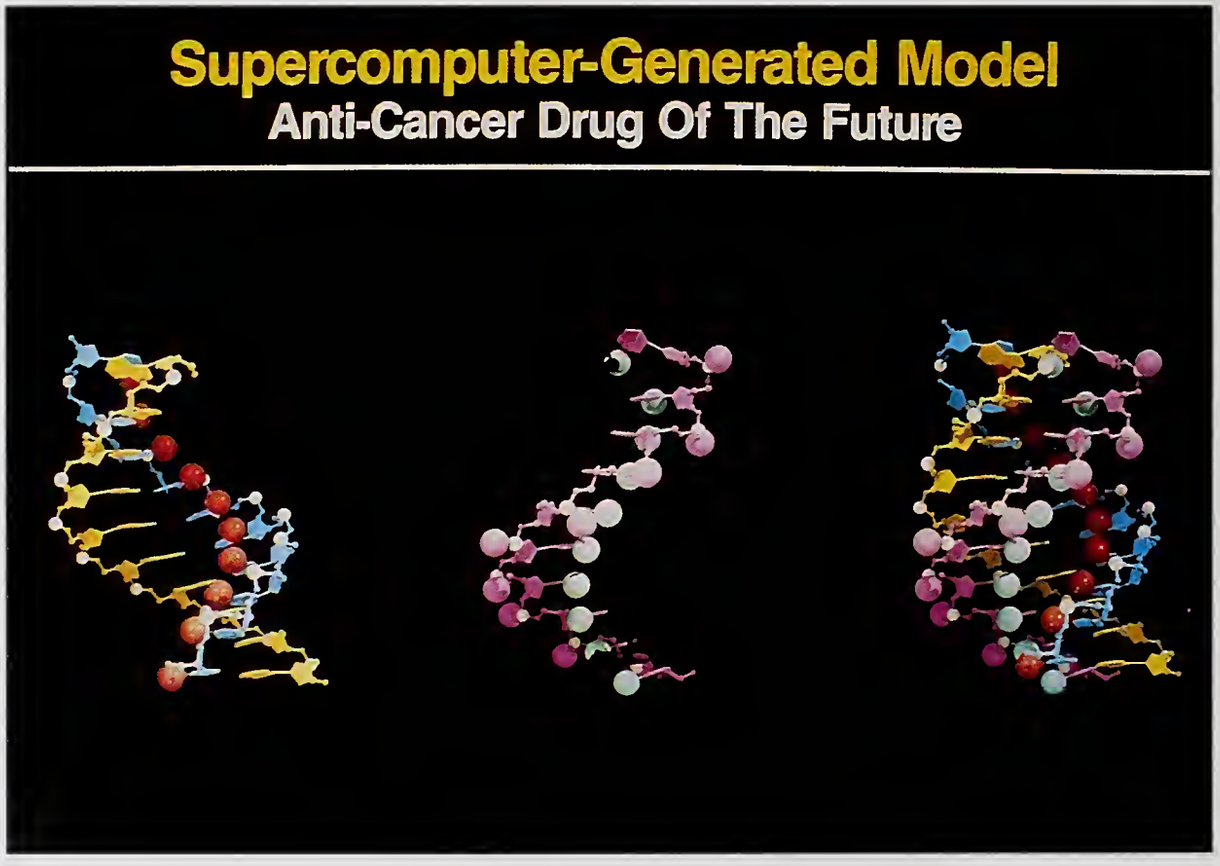
A Treatment Advance for Colon Cancer. Late in 1989, clinical trials conducted by NCI clinical cooperative groups demonstrated that postsurgical adjuvant treatment with 5-fluorouracil (5-FU) and levamisole greatly improves the survival of patients with Dukes' C colon cancer (Stage III, where microscopic deposits of cancer cells have spread to adjacent lymph nodes). Of the more than 110,000 people each year who have colon cancer, 21,000 are diagnosed with Dukes' C stage. This therapy reduced mortality by one-third, the most persuasive demonstration to date of a curative therapy for these patients. NCI mailed more than 40,000 clinical updates to promote rapid adoption of this highly beneficial treatment

into medical practice. NCI's designation of a special drug status made the 5-FU and levamisole therapy available in May 1989. These measures have contributed to rapid adoption. In less than 1 year from publication of the research findings, 40 percent of eligible patients are receiving this treatment. Use of 5-FU and levamisole adjuvant therapy for Dukes' C colon cancer received full FDA approval in 1990.

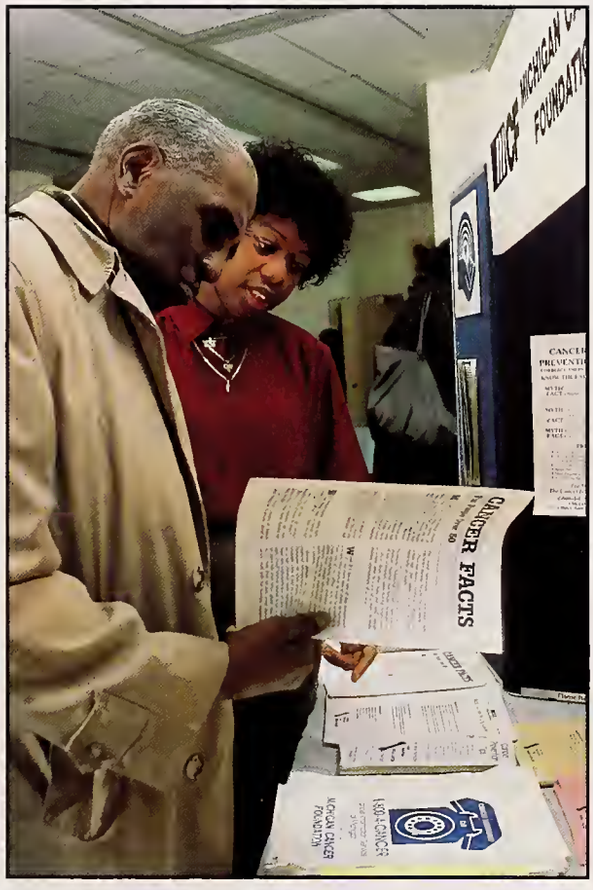
Research Opportunities

The Supercomputer in Cancer and AIDS Research. NCI uses supercomputer technology to generate knowledge about the functioning of cancer cells and the human immunodeficiency virus (HIV). Scientists can use the supercomputer to generate three-dimensional models of products from a virus or cancer cell and subsequently identify effective drug structures complementary to the shape of the target site. No other technology can readily execute the necessary calculations. The NCI supercomputer can perform three-dimensional modeling from the genetic information that codes for a gene product, thereby saving the time and costs associated with defining the structure in the laboratory. The determination of the structure of the HIV protease molecule has been particularly exciting because it has enabled drug companies to pursue a new class of anti-HIV compounds: protease inhibitors. Because the use of the supercomputer by NCI and other NIH researchers, and by extramural scientists is increasing, Congress appropriated funds for the acquisition in 1990 of an upgraded supercomputer, a machine with more processors and vastly increased memory capability. NCI is seeking collaboration with the drug industry to expedite the application of supercomputer technology.

Genetic Modification of Immune Cells. Following the initial studies of genetically altered TIL's, investigators are inserting genes coding for proteins that can potentiate the body's defense mechanisms. The gene for tumor necrosis factor has been introduced into human



TIL's as a possible means of increasing the concentration of an antitumor substance at the tumor site. Genes for other cytokines (cellular regulatory factors) such as alpha interferon and interleukin-2, which enhance the activity of TIL's, and genes that would direct TIL's toward their target cells will also be inserted. Lymphocytes may also be suitable vehicles for introducing genes that can treat a variety of hereditary diseases. NCI researchers and their collaborators have requested approval for the first gene therapy in humans for an inherited disorder. Cells genetically engineered to produce adenosine deaminase (ADA) will be used to treat children with an inherited deficiency in the production of this enzyme, which is linked to severe combined immunodeficiency disease in children.



Nationwide smoking cessation programs are among the National Cancer Institute's multifaceted cancer prevention efforts.

Policy Issues

Cancer Centers Program. The NCI Cancer Centers Program provides core support for multidisciplinary cancer research in a variety of institutions throughout the country. The National Cancer Advisory Board Subcommittee on Cancer Centers and NCI have reviewed and redefined the essential characteristics of a comprehensive cancer center. The new guidelines, which took effect January 1, 1990, reflect the priorities of the National Cancer Program and respond to congressional intent. These guidelines clarify the responsibilities of comprehensive centers in the areas of basic, clinical, and prevention and control research; technology transfer; high-priority clinical trials; training and education; information dissemination; and community service and outreach. Designation as a comprehensive cancer center will become an integral part of the peer review process. NCI hopes to encourage more centers to achieve comprehensive status. As recommended by the Institute of Medicine in a report submitted to Congress and NIH in 1989, NCI is developing a 5-year plan to reevaluate and strengthen the Cancer Centers Program with particular attention given to the relationship of cancer centers to each other and to NCI.

Construction Program. The NCI Construction Program has historically helped maintain a strong infrastructure for basic and clinical research throughout the country. New research initiatives cannot be undertaken without adequate and safe facilities. No funds were available for construction grants in fiscal year (FY) 1989, but in FY 1990, Congress authorized NIH to reserve funds from the institutes' appropriations to be used for extramural construction grants, from which NCI has received $2 million and may receive more.

National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS. This committee, chaired by Dr. Louis Lasagna, was established by the President's Cancer Panel in 1988 at the request of then Vice President George Bush. The committee was asked to study making therapies for cancer and acquired immunodeficiency syndrome (AIDS) available more rapidly by examining possible barriers to approval of new drugs. It has also addressed the problems of Federal and private third-party payers' denial of reimbursement for investigational therapies and for "off-label" use of some cancer and AIDS drugs. Coverage denial can in some cases slow NCI-sponsored clinical research and severely hamper the development of promising new therapies. The committee has stated in public its view that third-party payers should provide reimbursement for the nonresearch patient care costs of peer-reviewed, scientifically sound clinical trials. A full committee report is expected in the summer of 1990.

Cancer Prevention Through Smoking Cessation Interventions. The significant decline in lung cancer deaths in some age groups has been achieved primarily through reduced smoking. However, smoking remains a significant health risk, especially among women and minorities. In 1991, NCI plans to launch a major initiative based on the results of nearly a decade of clinical research on smoking cessation and prevention and on the results of an ongoing clinical trial of community-based smoking cessation strategies. The new program, the American Stop Smoking Intervention Study (ASSIST), will be conducted in cooperation with the American Cancer Society and State and local health agencies. It is expected to involve up to 20 States or large metropolitan areas and will reach up to 50 million Americans.

Patterns of Care Study. In addition to an ongoing evaluation of patterns of care in community hospitals and plans for studies in selected Surveillance Program contracts, the NCI has worked with outside experts to develop a more extensive study of the delivery of cancer treatment and whether state-of-the-art cancer therapies are reaching all people who need them. A concept for this initiative, which is responsive to a Congressional mandate (P.L. 100–607, sec. 413), will be reviewed in September 1990 by the Board of Scientific Counselors for the Division of Cancer Prevention and Control.

National Institute of Child Health and Human Development

Director's Preface

The National Institute on Child Health and Human Development (NICHD) conducts and supports research on the reproductive, developmental, and behavioral processes that determine the health of children, adults, families, and populations. To pursue this mission, NICHD administers a multidisciplinary program of research, research training, and public information. The ultimate objective of NICHD is to ensure that every child has the opportunity to fulfill his or her potential for a healthy and productive adult life.

Population Research

NICHD's Center for Population Research is responsible for the primary Federal program in population research.

Reproductive Sciences. Recent research suggests that there is a relationship between the presence of sperm antibodies in a woman's sera and an increased risk of either failure to conceive or increased miscarriages during the first trimester of pregnancy.

Contraceptive Development. Researchers are investigating Capronor (a biodegradable implant that releases a female contraceptive); skin patches for transdermal delivery of female contraceptives; a disposable, spermicide-releasing diaphragm; levonorgestrel butanoate (a long-acting injectable female contraceptive); a testosterone ester that functions as a long-acting injectable male contraceptive; Antide (a male contraceptive and treatment for female infertility); Ovablock (for female sterilization by tubal occlusion); and new condoms and spermicides.

Contraceptive Evaluation. Investigators found that the latex condoms available on the American market provide a substantial degree of protection from human immunodeficiency virus (HIV) and that using spermicide with condoms reduces the amount of viable virus leaking from damaged condoms.

Demographic and Behavioral Sciences. An investigator studying the effectiveness of sexuality education programs found that teenagers participating in the programs were no more likely to have sexual intercourse afterward than those who had not participated. However, among those who had intercourse, there were significant increases in the use of contraceptives among those exposed to sexuality education.

Research for Mothers and Children

Research supported by the Center for Research for Mothers and Children addresses questions related to low birth weight, mental retardation, learning disabilities, congenital malformations, abnormal physical growth, and acquired immunodeficiency syndrome (AIDS) in children, adolescents, and mothers.

Pregnancy and Perinatology. Studies have shown that maternal bed rest improves the status of the intrauterine

growth-retarded fetus, and that glycemic control in insulin-dependent diabetic mothers improves pregnancy outcome and lowers the risk of birth trauma and the rate and severity of macrosomia.

Mental Retardation and Developmental Disabilities. Research has led to the cloning of two genes on chromosome 21 (genes that when present in triplicate cause Down syndrome). The injection of these genes into a mouse has caused the animal to express some of the characteristics of the syndrome. Other investigators have succeeded in cloning the gene that is abnormal in individuals with phenylketonuria (PKU) and expressing the gene in cells in tissue culture as well as in a mouse model. These researchers are continuing to work with animal models in their investigations of this potential gene therapy for PKU.

Human Learning and Behavior. The first two learning disabilities research centers were established in fiscal year (FY) 1989, and a third will be established in FY 1990. Researchers supported by the Institute have amassed evidence that a chromosomal anomaly is linked to one or more forms of dyslexia. In addition, the Institute continues to support research focused on lowering the rate of childhood injury.

Genetics and Teratology. Investigators have developed animal models that will help elucidate the basic mechanisms of normal and abnormal development in a lethal megacolon condition, in congenital limb defects, and in human spina bifida.

Endocrinology, Nutrition, and Growth. A recent study has found that pregnant urban black women tend to have low levels of serum ferritin, which may relate to their high rate of bearing low birth weight babies. Other studies have identified markers for adult cardiovascular disease in adolescent males, have suggested that supplementing maternal diets with protein and calories may reduce osteopenia among low birth weight babies, and have indicated in animal models that maternal diets deficient in vitamin B_6 may interfere with brain development in the progeny.

Pediatric, Adolescent, and Maternal AIDS. In this new program area, a study of the natural history of the transmission of HIV from mother to child has found that the transmission rate is approximately 30 percent, that children born to HIV-infected mothers weigh less than children born to uninfected mothers, that gains in height and weight in the first 6 months after birth are significantly smaller, and that the mean head circumference is significantly smaller when measured at 3 months and 6 months. Additional analysis of certain serologic measures in this cohort of mothers and children demonstrated that mothers who did not transmit HIV to their infants possessed a high reactivity against the HIV envelope glycoprotein (gp120), whereas mothers who did transmit had little or no reactivity against this protein. These serologic findings have important implications for vaccine development and immunotherapy.

The Institute's nationwide network for HIV clinical trials in children is being linked to that of the National Institute of Allergy and Infectious Diseases. Through this merged network, state-of-the-art HIV therapeutic research and care will be available to the majority of HIV-infected children and pregnant women in the United States.

Prevention Research Program

The Prevention Research Program assures that high priority is given to studies related to preventing infant mortality, low birth weight, congenital malformations, mental retardation, and other conditions related to the health of mothers, children, and the population. A major study supported by the Institute has found that chorionic villus sampling, a new

procedure to test for genetic abnormalities earlier in pregnancy than possible by amniocentesis, is a safe, effective technique. Two followup studies of children indicate that those who received chloride-deficient formula in infancy are not significantly different from their peers in physical or intellectual development at 9 and 10 years of age, and that children born through in vitro fertilization face no greater risk of congenital malformation or developmental delay than other children. A recent study suggests that neither multivitamin nor folate supplements prevent neural tube defects. Results from the Diabetes in Early Pregnancy Study indicate that women with insulin-dependent diabetes who maintain good metabolic control are not at increased risk for pregnancy loss or for bearing a macrosomic infant.

Intramural Research

The Intramural Research Program conducts research on the biomedical and behavioral aspects of human development and makes a significant contribution to the future prevention of developmental and reproductive disorders through the research training it offers to young clinical and basic research scientists.

Vaccines. NICHD scientists have developed a new, highly purified pertussis toxoid vaccine, which induces higher antibody titers with fewer side effects than the current whole-cell diphtheria-pertussis-tetanus vaccine. Preliminary results of tests in infants are extremely promising. A new *Hemophilus influenzae* polysaccharide vaccine, conjugated to protein to increase its immunogenicity, has been studied in infants as young as 2 months of age (the group experiencing the most serious infection with this organism that often leads to mental retardation). The vaccine was highly effective in pilot studies and is now in field trials. Other conjugate vaccines being investigated include those for typhoid fever, pneumococcal pneumonia, *Shigella* dysentery, and Staphylococcus infections in newborns.

Developmental Neurobiology. One of the most striking features of the nervous system is the formation of orderly connections among nerve cells during normal development, but how this orderliness is achieved has been enigmatic. NICHD neurobiologists believe that electrical signals among the nerve cells might affect their physical connections; to address this question they have succeeded in isolating and growing part of the circuitry of the developing nervous system in the laboratory. This model will enable scientists to study normal and disordered relationships among nerve cells in the brain and the roles of experience and the environment in brain development.

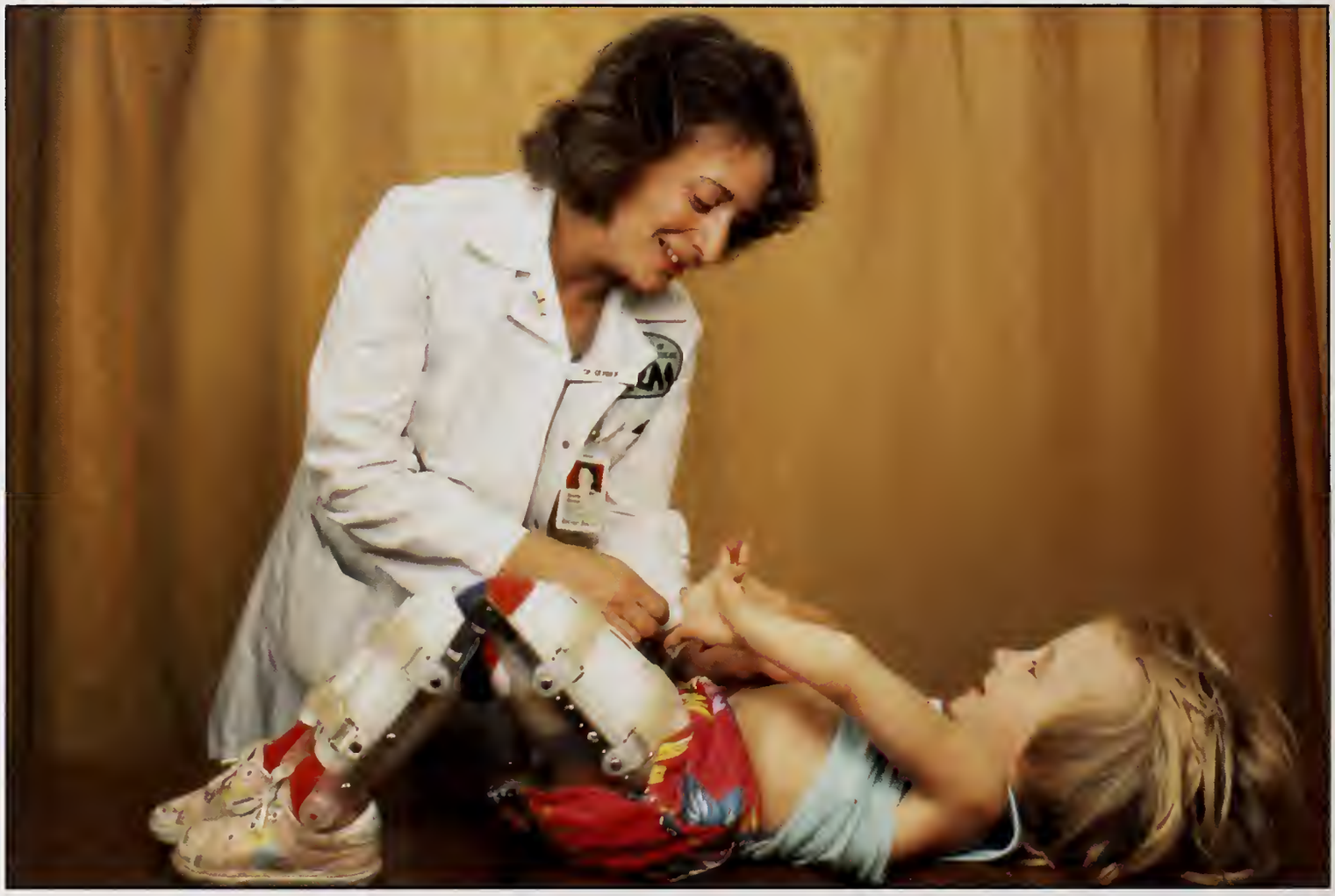
Molecular Genetics. Other intramural scientists studying molecular mechanisms that control the early development of the nervous system have succeeded in isolating and identifying five neurospecific genes, expressed in the earliest stages of embryogenesis, in a frog model. This achievement is an important step in understanding the normal development of the vertebrate brain and central nervous system.

Cell Biology and Metabolism. Intramural scientists have discovered in the genes unique structures that control iron metabolism. Fusing these iron-responsive elements to any gene makes that gene's expression exclusively dependent on the level of iron in the cell containing the gene. This discovery is important not only to researchers studying iron metabolism during infant development and in pregnancy, but also to scientists in the biotechnology industry as a means of regulating gene expression.

Day Care. In another study, NICHD scientists are studying the effects of different types of infant care arrangements (home care, family day care, and center-based day care) on social, personality, and intellectual development. Results

indicate that the type of care arrangement by itself is not associated with major differences in child outcome measures during the toddler and young childhood years. In contrast, the quality of the care, the infant's temperament (apparently

spectrometer to measure how the body uses calcium, leading to a safer and more precise way to assess the needs of premature babies who need extra calcium; the development of molecular probes that assist in diagnosing genetic defects in the



NICHD research has increased our understanding of the defects in collagen which result in such conditions as osteogenesis imperfecta (brittle bone disease).

determined genetically), and the social support systems available all show significant effects.

Other Advances. Other advances include increased understanding of the potentially noxious role of certain neurotransmitter receptors when the brain is deprived of oxygen, as in strokes or difficult births, and the roles of various amino acids in regulating the activity of these receptors; the use of the mass

structure and function of collagen (a major protein of bone and skin), which lead to conditions such as osteogenesis imperfecta (brittle bone disease); and several accomplishments important to AIDS research, such as the development of a transgenic mouse, which can be used as a model to study factors that induce or inhibit HIV replication in cells and improve understanding of the pathogenesis of AIDS dementia.

Promising Research Opportunities

Promising research opportunities abound in the NICHD programs. The following examples illustrate the high degree of relevance that NICHD programs have to current concerns about the rate of infant mortality and birth defects in the United States, minority health, adolescent health, mental retardation and learning disabilities, and AIDS.

Soon results will begin coming in from the joint clinical research protocols being conducted in the Maternal/Fetal Medicine Unit and the Neonatal Intensive Care Unit networks established in 1986 and from a study currently under way that will provide better understanding of ethnic differences in the rate of low birth weight. Ambitious research agendas for sudden infant death syndrome and prevention of childhood injury are in the early stages of implementation. The effectiveness of deinstitutionalizing and mainstreaming mentally retarded individuals is being studied and a major conference on the topic is scheduled for 1991. NICHD looks forward in 1990 to increased progress in research in reproductive medicine as a result of the planned formation of a reproductive medicine network and to increased numbers of pediatric researchers as a result of the funding of the first child health research centers. Other promising research opportunities include two projects currently in the developmental stages that will evaluate the effectiveness of providing outreach and case management for high-risk pregnant women and evaluate the effectiveness of various interventions in preventing teenage pregnancy. NICHD is sponsoring a clinical trial of the efficacy of intravenous immunoglobulin in reducing serious bacterial infections in children with AIDS and is planning new studies of the role of the placenta in transmitting HIV infection from mother to child.

Intramural scientists are conducting a clinical trial of supplemental genetically engineered growth hormone to increase the adult height of children with non-growth-hormone-deficient short stature, a condition affecting 1 million children in the United States.

National Institute on Deafness and Other Communication Disorders

Director's Preface

In October 1988, the National Institute on Deafness and Other Communication Disorders (NIDCD) became the 13th Institute mandated by Congress in NIH. NIDCD conducts and supports research and training on normal mechanisms as well as disorders of hearing and other communication processes, including diseases affecting hearing, balance, smell, taste, voice, speech, and language. The Institute also conducts and supports research and training related to disease prevention and health promotion and to the special biomedical and behavioral problems associated with communication impairments and disorders. NIDCD supports efforts to create devices that substitute for lost and impaired sensory and communication functions and to collect and disseminate information to health professionals, patients, industry, and the public on research findings in these areas.

Today's tools of communication are extraordinarily sophisticated. Effective communication is the most important factor in an individual's ability to function productively in our society. NIDCD is striving to maximize the benefits of research advances and to make available the latest technology to Americans who would most benefit from its technology. NIDCD makes every effort to ensure that the latest information from research is known to the public, medical professionals, and other scientists.

Research Progress and Accomplishments

Hearing and Deafness

More than 28 million Americans are believed to have some degree of hearing impairment. This estimate includes approximately 2 million persons who are profoundly deaf. One of every 1,000 infants is born deaf, and several times this number have a substantial impairment by the age of 3. The most common cause of temporary hearing loss is otitis media, which is predominantly a disease of infants and young children. In a recent survey, this disease accounted for 10 million visits to physicians' offices a year and an unknown number of prescriptions for antibiotics. The estimated health care costs for otitis media in the United States exceed $1 billion per year. At the other end of the age spectrum, more than one-third of the population has a significant hearing impairment by age 65, and the prevalence of age-related hearing impairment (presbycusis) increases rapidly with increasing age. These numbers are expected to increase substantially as longevity is extended. Hearing impairment is associated with considerable suffering for affected individuals and their families. NIDCD is striving to stimulate additional research on hearing impairment and deafness and to overcome a long history of societal discomfort and ignorance about deafness.

Noise. Research on noise exposure (the most common preventable cause of hearing loss today) has been targeted by NIDCD for particular emphasis and focus. NIDCD and the NIH Office of Medical Applications of Research cosponsored a consensus development conference on noise and hearing loss at the NIH on January 22-24, 1990. The statement drafted by the conference panel provided

recommendations and avenues for future research. NIDCD is also developing a major public education campaign to advise the public on this preventable form of hearing loss.

Cochlear Implants. Implantable electric prostheses (cochlear implants) have opened a world of sound to thousands of deafened adults. Applying the latest technological tools available, NIDCD-supported researchers are continuing to develop diagnostic procedures to predict a person's ability to benefit from an implant, methods of optimizing speech processing strategies, and design and fabrication of new types of auditory prostheses.

Usher's Syndrome. Usher's syndrome, characterized by congenital deafness, progressive visual impairment leading to blindness, and often mental retardation, may account for as many as 10 percent of all congenital deafness, or 200,000 persons. In a significant advance in this field, NIDCD researchers recently located the Usher's gene on chromosome 1.

Voice, Speech, and Language

An estimated 14 million children and adults in the United States suffer from speech and language disorders. Voice disorders cause hoarseness and limited loudness and pitch ranges. Speech disorders involve any aspect of how words are spoken, including correct production of speech sounds, intonation, and fluency; the most frequent speech disorders are articulation errors and stuttering. Language disorders reflect difficulty in understanding what is said and in using words and sentences to communicate.

New Therapy for Papillomavirus Infections. Papillomavirus infection of the larynx and upper respiratory tract is a serious disease that affects both children and adults and can cause a life-threatening obstruction of the airway. Patients with this infection develop recurrent wartlike growths that used to be treated by frequent surgical removal. This method was not entirely satisfactory, however, because a scarring often developed. Other conventional and experimental therapies have failed to cure this disease. In an exciting advance, a new creative treatment—a photodynamic therapy—has been found to be much more effective for recurrent papillomavirus infection in the upper respiratory tract, eliminating the need for repeated operations.

Stroke. Recent research has uncovered the value of medical treatment of the language problems following stroke in some patients. One complication of stroke in these patients is the loss of the ability to make sense of language. Researchers have determined that this disability may reflect disruption of specific neurotransmitter systems. Treatment of adults with hesitancy and impaired initiation of speech included use of dopamine agonist (bromocriptine). Language performance notably improved during this therapy, suggesting that this pharmaceutical agent may be beneficial in treating selected symptoms of stroke.

Balance

Millions of Americans aged 17 and older have experienced dizziness or balance problems. In the United States, there are an estimated 97,000 new cases each year of Meniere's disease, a disorder that affects the inner ear and causes episodes of vertigo, fluctuating hearing loss, and tinnitus (ringing in the ears). Several groups of people are particularly at risk for balance disorders. Most people older than 70 report problems of dizziness and imbalance, and balance-related falls account for more than one-half of accidental deaths in the elderly. Furthermore, in a sample of persons aged 65 to 75, one-third reported that dizziness and imbalance degraded the quality of their lives.

New Technology. Researchers have employed the latest computer technology to develop new methods to detect, quantify, and localize the source of vestibular disturbances. Powerful rotational devices

now make it possible to assess the capacity of the vestibular system to stabilize vision during the head movements of daily living.

Smell and Taste

An estimated 10 million Americans have smell and taste disorders. The predominant problem is the natural decline in the ability to smell, which typically occurs after age 60. Some people are born with chemosensory disorders, but most develop them after an injury or illness. Chemosensory disorders may result from polyps in the nasal or sinus cavities, hormonal disturbance, or dental problems. Loss of smell and taste can also be caused by prolonged exposure to certain chemicals such as insecticides and by some medicines. Many patients who receive radiation therapy for cancers of the head and neck have disturbances in smell and taste. A person with faulty senses of smell and taste is deprived of an early warning system that most of us take for granted. The senses of smell and taste alert us to fires, poisonous fumes, leaking gas, and spoiled foods.

Nervous System Regeneration. Findings about the nasal olfactory epithelium have profound implications not only for the olfactory neurosystem but for the repair and rejuvenation of the nervous system in general. The nasal olfactory neuroepithelium is known to have the unique capacity to regenerate receptor neurons from precursor cells throughout life. NIDCD-supported researchers have recently discovered that this neuroepithelium produces another type of cell that migrates into the brain during adult life. Thus, the olfactory neuroepithelium is not only a source of olfactory receptor neurons, which have a powerful effect on the brain, but also a direct source of additional cells for the brain.

Changes in the Sense of Smell in the Elderly. NIDCD-supported researchers have developed a very useful test for measuring the sense of smell that made it possible to test the sense of smell across the age span. The observation that at all ages females have a more acute sense of smell than males was confirmed. A striking finding was that at age 65 the sense of smell begins to decrease. The loss of the sense of smell parallels the loss of the senses of vision and hearing. The data derived from this test allow a patient who has lost the sense of smell to be compared to the normal range for his or her age—a comparison that has been very useful in treating these disorders.

Laboratory of Molecular Otology

For the past several years, laboratories around the world have been racing to clone one or another of the various types of glutamate receptors present in the brain. They form a class of proteins responsible for excitatory transmission between neurons. Three groups of scientists, one of which is directed by an NIDCD intramural scientist, recently reported cloning sequences of receptors that specifically bind kainate, a well-known glutamate analog. This is a breakthrough because glutamate is the main excitatory neurotransmitter in the brain and every neuron has receptors for it.

Speech and Voice Unit

Investigators in the NIDCD intramural Speech and Voice Unit demonstrated a successful treatment for two voice disorders: Botulinum toxin injections have proven effective in treating voice tremor and spasmodic dysphonia.

Audiology Unit

The Audiology Unit is involved in multidisciplinary protocols and studies patients from 11 of the NIH institutes. One example of its studies is related to the neurofibromatoses in which important audiologic findings have been reported.

Future Opportunities

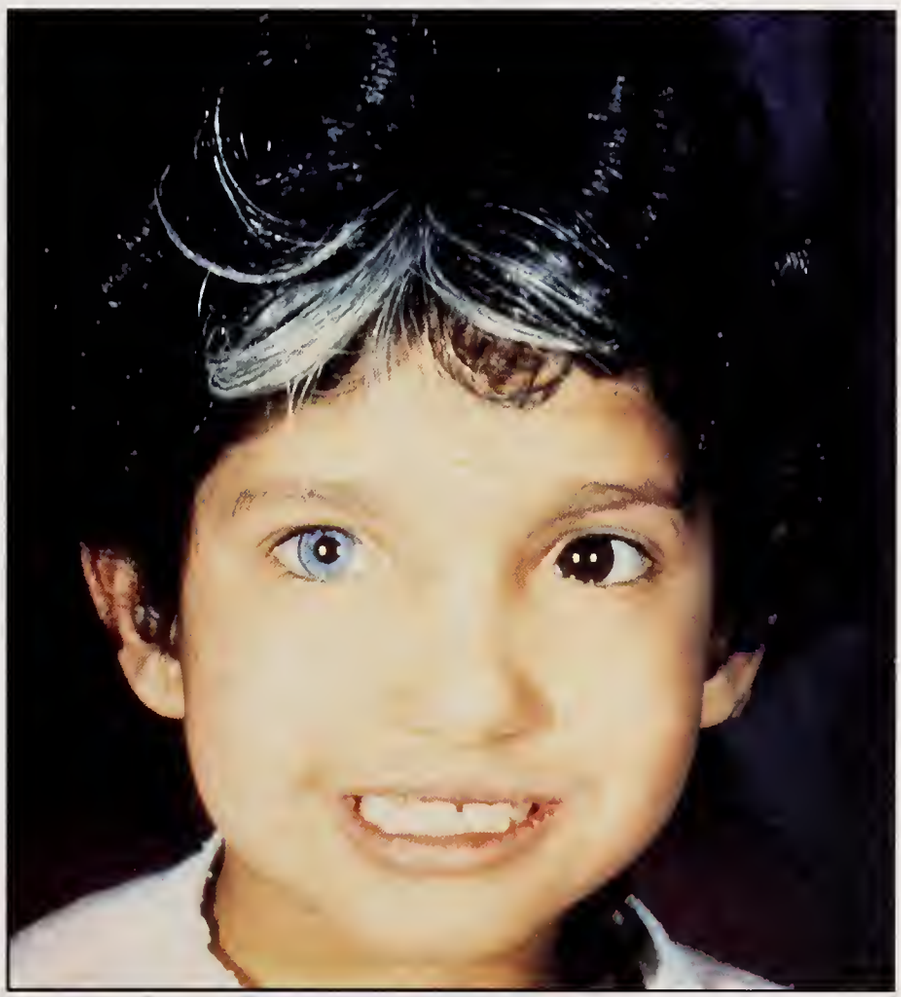
Multipurpose Centers. The legislation that established NIDCD (Public Law 100-553) mandated that the Institute provide for the development, modernization, and operation of national multipurpose research and training centers. The Institute anticipates the award of three to five of these multidisciplinary centers in fiscal year 1990. The goals of these centers are to support basic and clinical research, perform research training, provide continuing education for health professionals, and disseminate information to the public in one or more of the program areas of the Institute.

Research Training and Career Development. The National Strategic Research Plan of NIDCD recommended that "a first priority of the new institute should be to address this critical shortage of research personnel and training support" by developing a plan for fostering a "community of investigators dedicated to advancing research on human communication and its disorders." A limited number of trainees and fellows are currently receiving support at the predoctoral level in sciences related to hearing, speech, and taste. In July 1989, NIDCD convened a panel of expert consultants to identify research training activities that could be implemented by NIDCD in the next one to 2, 5, and 10 years. A number of these recommendations have been implemented. Special emphasis will be placed on targeting underrepresented minorities and communicatively impaired individuals.

Information Clearinghouse. The legislation that established NIDCD mandated the formation of an information clearinghouse, an Institute resource where the results of the latest studies in the NIDCD program areas could be made available to health professionals, patients, industry, and the public.

Otitis Media Clinical Trial. Half of all children have ear infections before they reach their first birthday, and 9 out of 10 children have had ear infections by the time they are 6 years old. Otitis media is the leading cause of acquired hearing loss before age 10. Anatomic, physiologic, genetic, and environmental factors contributing to the development of this disease are under investigation. The NIDCD, in cooperation with the National Institute of Allergy and Infectious Diseases and the National Institute of Child Health and Human Development, will issue a solicitation for research institutions to study a family of vaccines and determine their effectiveness in the targeted population of children with early, recurrent otitis media.

Genetic Studies. Genetic factors are known to cause more than 60 percent



Waardenburg Syndrome is one of the most common syndromic causes of hereditary deafness. This deaf child's illness is also characterized by a white forelock and widely spaced eyes of different colors.

of all cases of severe childhood deafness. The impact of heredity on late-onset hearing impairments is mostly unknown, but it is thought to be considerable. One in every 1,000 children is congenitally deaf, and genetic disorders are responsible for at least half of these conditions. Using recently developed techniques in molecular biology and genetics, it is now possible to map the genes whose mutations cause hearing impairments. Mapping genes is the first step toward finding out how they work, what proteins they cause to be manufactured, how they produce hearing impairment, and consequently how early diagnosis, prevention, or treatment might be achieved. Geneticists, otolaryngologists, and audiologists around the country have been asked to provide contacts between intramural scientists and families with genetic hearing impairment. Blood samples from individuals from these families will be collected for extraction of DNA for molecular genetic studies. Initially, the focus will be on the mapping of the gene involved with Waardenburg Syndrome.

The NIDCD AIDS Program. Clinicians caring for patients with AIDS or AIDS-related complex report that the communication systems of these patients suffer the ravages of this disease. This aspect of AIDS has not been well documented or researched, however. Particularly in need of study are pediatric AIDS patients, who have shown significant morbidity in hearing, speech, and language. NIDCD will encourage studies of this challenging population.

Decade of the Brain. The NIDCD is an active participant in the NIH celebration of the Decade of the Brain and joins several other institutes at the NIH in emphasizing research on neurobiology.

National Institute of Dental Research

Director's Preface

In the 1987-88 biennial report to Congress, the National Institute of Dental Research (NIDR) reported dramatic improvements over the past few decades in the dental health of America's children and young adults. The reduction of disease in our younger citizens has resulted in an annual savings of $3 to $4 billion in the Nation's dental bill.

Unfortunately, older Americans are not enjoying the same improvements in dental health. More than 41 percent of men and women over age 65 are toothless. Older people have three times more decay on tooth roots than working-age adults, and gum disease is more prevalent and more severe in those over 65.

One of NIDR's major initiatives during the 1990's will be to duplicate in older Americans the impressive reductions in dental disease achieved in the young. With the goal of eliminating toothlessness, the Institute is spearheading the Research and Action Program for Improving the Oral Health of Older Americans and Other Adults at High Risk. Another major initiative will address the dental problems of special-care patients whose oral health has been compromised by underlying medical or handicapping conditions, as well as those receiving medical treatments that can harm oral tissues.

The Research Program

NIDR conducts and supports research on a wide range of oral health problems, including salivary disorders, craniofacial anomalies, tooth decay, periodontal diseases, and behaviors that jeopardize oral health. Institute researchers are looking at bone and other mineralized tissues, micro-organisms that invade oral tissues, and the immune responses that figure in oral health and disease. New technologies and information emerging from dental research laboratories are refining our understanding and treatment of the oral tissues—and the human organism as a whole.

Periodontal Disease. It is difficult for some handicapped individuals to perform normal oral hygiene procedures such as brushing and flossing. In a pilot study, investigators found that a mouth spray containing the antibacterial agent chlorhexidine improved the oral health of institutionalized mentally retarded adults with gingivitis. The researchers plan to expand their pilot test to other high-risk groups.

In clinical trials, an antibiotic treatment was shown to reduce the need for surgery in patients with chronic adult periodontitis, the most common form of periodontal disease. Patients who received a 1-week course of metronidazole and conservative dental care needed surgery on an average of five fewer teeth than patients given a placebo plus conservative care. The protective effects of metronidazole persisted throughout the 2- to 3-year followup.

In other studies, combination antibiotic treatment using metronidazole and amoxicillin improved the condition of patients with localized juvenile periodontitis, a relatively rare but severe gum

disease that affects teenagers and young adults. Conventional therapy fails in about a quarter of patients, and disease progresses to tooth loss. The combination treatment improved the patients' condition immediately and eliminated the causative organism.

Craniofacial Anomalies. A woman who smokes during the first trimester of pregnancy may place her unborn child at increased risk for cleft lip with or without cleft palate, NIDR-supported scientists have found. One in 700 babies born in the United States each year is afflicted with this birth defect, making it one of the five most common major malformations. The researchers examined Swedish birth records and maternal histories, which are known for their uniformity and clarity, and concluded from their analysis that smoking is one of the most important preventable risk factors associated with clefting defects.

Acquired Immunodeficiency Syndrome (AIDS). An important issue to be resolved is the role of saliva and the oral cavity in the transmission of the human immunodeficiency virus (HIV), which causes AIDS. The virus can be recovered from the mouth and has been found in saliva, yet neither the mouth nor saliva appears to be a route of HIV transmission. NIDR scientists have shown that human saliva can inhibit the ability of HIV to infect cells. This inhibitory activity has been found in all saliva samples studied, including those from healthy men, women, and children as well as from HIV-infected men. New studies are aimed at verifying these findings and determining exactly how saliva inhibits HIV infectivity.

Hairy leukoplakia, a whitish lesion that generally appears on the tongue, is (after candidiasis, a fungal infection) the second most prevalent oral complication of HIV infection. Because the presence of hairy leukoplakia is considered a reliable predictor of subsequent development of AIDS, NIDR is vigorously pursuing studies of its causes, early diagnosis, treatment, and prevention. Preliminary observations suggest that the lesion is caused primarily by the Epstein-Barr virus.

Dental Caries. Community water fluoridation is still the most equitable, cost-effective method for preventing tooth decay. NIDR's recent nationwide survey of dental health in schoolchildren showed that youngsters who were lifelong residents of fluoridated communities had 18 to 25 percent less tooth decay than children who were never exposed to fluoridated water.

Studies of decay-promoting bacteria have shown that certain bacterial proteins play a key role in the disease process. Investigators have now found that mutant forms of bacteria, which lack these proteins, do not promote decay in experimental animals, even when the animals are fed diets rich in sugar. The researchers are pursuing the possibility of developing safe forms of bacteria that could be introduced into the mouth to replace disease-causing bacteria.

Taste and Smell. Research is debunking a common generalization about aging and oral health: that food enjoyment, especially the sense of taste, diminishes in aging. NIDR investigators, in collaboration with scientists from the National Institute on Aging, have shown that healthy men and women, regardless of their age, are similar in their ability to discern the four basic taste modalities (sweet, sour, salty, and bitter). Older persons are as competent as younger ones in judging the texture and temperature of various foods, the researchers found. However, people over 65 do show impairments in the sense of smell. These studies suggest that, in healthy older persons, decreased food enjoyment likely reflects a diminished sense of smell.

Mineralized Tissues. Several years ago, NIDR scientists developed methods for growing human bone-forming cells in culture. These methods have allowed

Tooth Decay in U.S. Children by Age and Water Fluoridation Exposure			
Age	Life-long Water Fluoridation Exposure Mean DMFS*	No Water Fluoridation Exposure Mean DMFS*	Percent Difference
5	0.03	0.10	70
6	0.14	0.14	0
7	0.36	0.53	32
8	0.64	0.79	19
9	1.05	1.33	21
10	1.64	1.85	11
11	2.12	2.63	19
12	2.46	2.97	17
13	3.43	4.41	22
14	4.05	5.18	22
15	5.53	6.03	8
16	6.02	7.41	19
17	7.01	8.59	18
(All ages)	2.79	3.39	18

*Decayed, missing, or filled tooth surfaces (128 possible surfaces in children with all their permanent teeth)

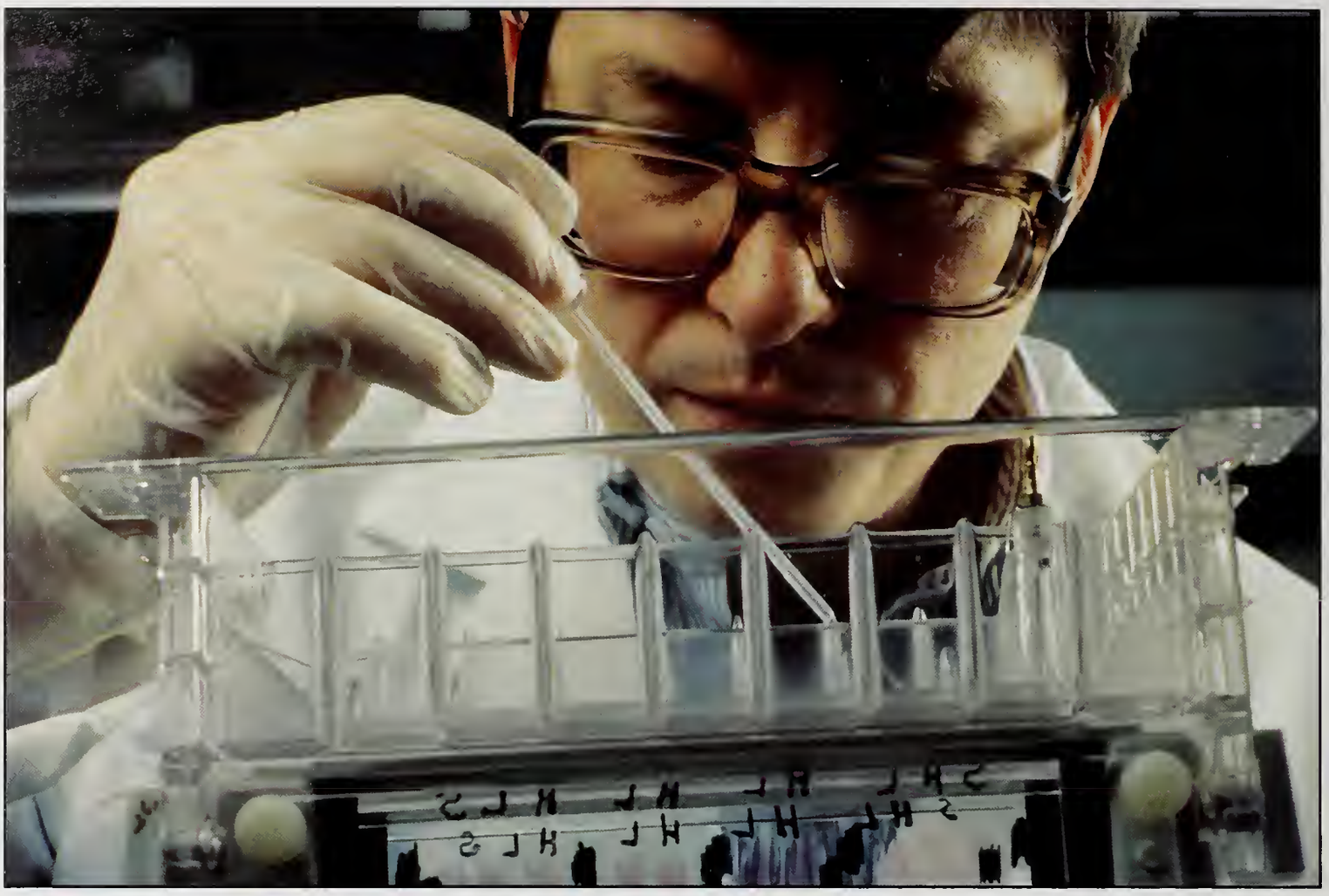
researchers to study the role of hormones and growth factors in bone formation. It has been shown, for example, that the female hormone estradiol directly affects the function of bone-forming cells; this finding provides a biochemical explanation for the role of estrogen deprivation in postmenopausal osteoporosis. In other studies, NIDR researchers have found that bone-forming cells from adult humans use a specific growth factor as a self-inducing growth regulator. This information provides a basis for exploring the role of specific growth factors in reversing the decline of bone cell function in bone-wasting diseases associated with aging.

Future Opportunities

Human Immunodeficiency Virus. In the 1990's, NIDR will continue to investigate the oral manifestations of HIV infection. Researchers will also examine the role of saliva in transmitting or inhibiting HIV and other disease-causing agents. Studies will range from basic investigations of the micro-organisms themselves to population studies of individuals at increased risk for HIV infection. These individuals will be examined for oral lesions and tested for the presence of antibodies to the virus.

Jaw Disorders. An estimated 5 to 10 percent of adult Americans suffer persistent pain or functional limitations in the temporomandibular (jaw) joint and its associated muscles. To stimulate much-needed research in this area, NIDR will be funding basic and clinical studies on joint and muscle pain, inflammatory pain, and pathophysiological and behavioral factors underlying jaw disorders. Other studies will determine the efficacy of various diagnostic and treatment procedures.

Racial and Ethnic Minorities. NIDR epidemiologists are designing a new



An NIDR investigator uses gel electrophoresis to separate salivary proteins.

project to study the oral health of racial and ethnic minorities in the United States. Using existing literature and data bases, researchers will determine what is known about the oral health of racial and ethnic minorities. Plans also call for new epidemiologic studies of selected minority populations. Scientists then will identify new research and action initiatives to improve the oral health of minority citizens.

Pima Indians of Arizona. NIDR will continue studies of the oral complications of diabetes in the Pima Indians of Arizona, who have the highest known prevalence of adult-onset diabetes in the world. Researchers have found that Pima Indians with diabetes are 15 times more likely to be toothless than those without diabetes. The major reason for their tooth loss is periodontal disease. In the next phase of their study, the researchers will characterize the specific bacteria associated with periodontal disease in these patients as well as their immune responses to the bacteria. They also will design treatments for this high-risk population.

Dry Mouth. Dry mouth, though not a disease in itself, can result from certain disorders and is a common side effect of many medical treatments. Patients with dry mouth can develop oral sores and infections and rampant tooth decay. Researchers are continuing their search for an ideal artificial saliva that would be long lasting, provide lubrication, inhibit colonization by disease bacteria, and coat the oral tissues for protection against environmental insult. NIDR researchers

are conducting studies to determine the structures of salivary molecules responsible for these protective functions in the mouth. Composite salivary substances with multiple functions could then be developed and even targeted to suit an individual patient's needs.

Issues and Policies

As with the oral health status of Americans, a dichotomy exists with regard to research. Although there are more research opportunities than ever before, investigators face ever-increasing competition for available funds. The challenge, then, is to make the most of every research dollar spent. To meet this challenge, NIDR has developed a long-range research plan for the 1990's. In a departure from earlier plans, this one establishes research priorities that include studies of systemic medical disorders, such as diabetes, that harm oral tissues; studies of oral health problems, including oral cancers and certain pain problems, that merit increased attention; implementation of the Research and Action Program for Improving the Oral Health of Older Americans and Other Adults at High Risk; and efforts to finish the job of eliminating tooth decay and gum diseases as major oral health problems. To facilitate these activities, Institute plans call for new and expanded collaborations with health professional and voluntary organizations and other consumer groups, Government and private research organizations, and the private sector. Special efforts will be undertaken to improve the oral health of ethnic and racial minority groups and to recruit minorities to careers in oral health research. At the same time, broad-ranging basic research will be encouraged to allow investigators to pursue ideas that may well signal the next revolution in biomedical research.

National Institute of Diabetes and Digestive and Kidney Diseases

Director's Preface

November 22, 1990, is the 40th birthday of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Research on the diseases and medical subject areas for which NIDDK is responsible—diabetes and endocrine and metabolic diseases; digestive diseases and nutrition; and kidney, urologic, and hematologic diseases—ranges from fundamental science to clinical trials of new therapies. The focus on basic research that has traditionally guided NIDDK's programs is grounded in the facts that a fundamental understanding of the intrinsic nature of each disease is imperative for the development of effective strategies for prevention and therapy and that the work of the Institute involves many

The Pima Indian Reservation near Phoenix, AZ, is the site of important clinical studies.

chronic and progressive diseases with as yet unknown etiologies.

Institute efforts are planned and coordinated through an extramural support program that provides funding for research at more than 400 non-Federal universities, clinical facilities, and research institutions across the country and abroad, and through an intramural component, which focuses on research conducted primarily in NIDDK's laboratories and clinical facilities on the NIH campus in Bethesda, MD, and at field stations in and near Phoenix, AZ.

Highlights of Research Advances

The interrelated nature of NIDDK programs ensures close, continual cooperation among its branches and divisions; the interdisciplinary nature of the research necessitates a highly coordinated effort in planning and conducting the work. In addition, several activities are common to all parts of the Institute and require joint consideration. This section highlights a few of the areas in which NIDDK has reported recent progress.

Insulin-Dependent Diabetes Mellitus (IDDM). Progress toward finding sensitive, specific, and reliable markers of this type has been reported: a genetic marker of susceptibility was found, and antibodies against a 64 kilodalton (molecular weight) antigen of the beta cell have been described; both of these findings serve to identify those who will develop IDDM so that early intervention measures can be taken.

Non-Insulin-Dependent Diabetes Mellitus (NIDDM). In new research that sheds light on the action of insulin, the gene coding for a distinct insulin-controlled, extracellular glucose transporter protein has been identified. In addition, in the insulin receptor itself, a point mutation in only one DNA base has been found to affect the function of the tyrosine kinase component; in obese NIDDM patients the tyrosine kinase defect is reversible after weight reduction. Another point mutation has been found to impair internal cell processing of the receptor and its movement to the cell surface to assume its insulin-binding role at the cell wall.

Obesity, Fat Cell Adipsin, and the Immune System. Adipsin is a protein unique to the fat cell. It is secreted into the circulation and appears to have a regulatory role in energy metabolism. Tests show it to be a homolog of one of the components of the immune complement system (human factor D) and thus one of several examples of immune system components with catabolic effects on fat cells (e.g., tumor necrosis factor and some cytokines).

Growth Hormone (GH) Deficiency. Injection of the hypothalamic GH-releasing hormone (GHRH) stimulates growth, as does GH itself. GHRH, a smaller molecule than GH, is easier to administer and less expensive. Recent clinical trials demonstrate that therapeutic results of GHRH are equivalent to those of GH by several routes of administration. New therapeutic agents based on the GHRH structure are under development.

Hyperparathyroidism. The diagnosis and treatment of hyperparathyroidism have been improved by the development of a two-site immunoradiometric assay for parathyroid hormone. This assay has succeeded in completely separating the hypercalcemia of hyperparathyroidism from that due to malignancy or other causes. A modified form of the assay allows results in 15 minutes, so it can be performed during surgery. The assay can be used to distinguish single adenomas from multiple hyperplasia, eliminating unnecessary bilateral neck explorations as well as reoperation for missed hyperplasia sites.

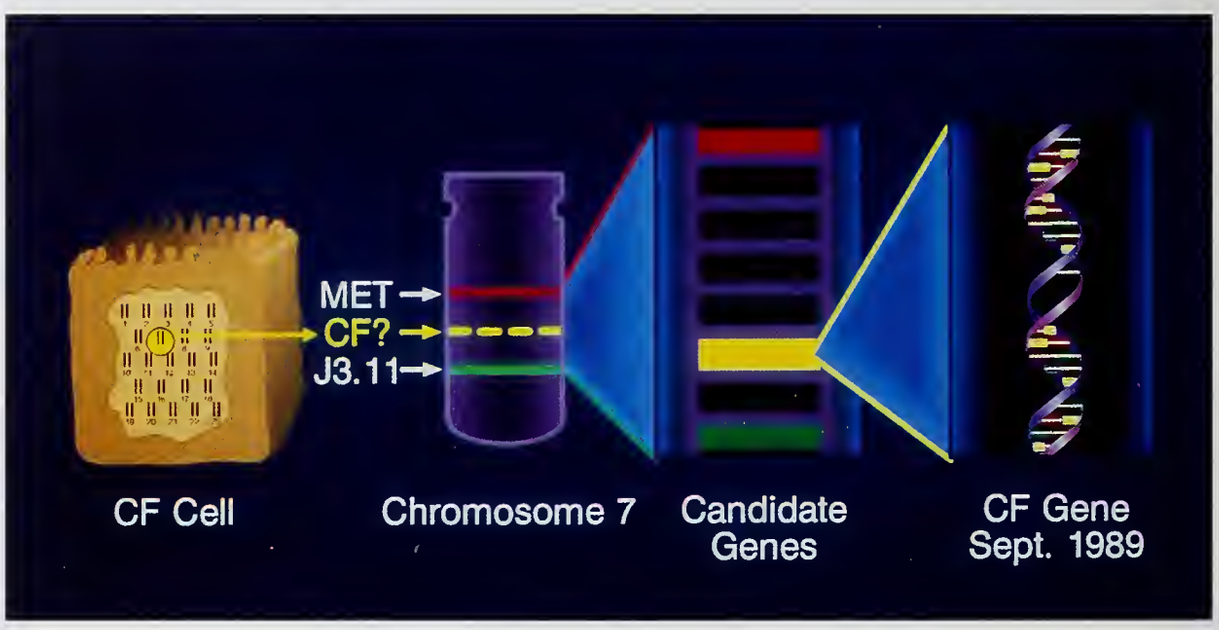
Osteoporosis. Impairment of parathyroid hormone secretion has now been shown to result in decreased renal activation of vitamin D. Previous studies show that renal responsiveness to parathyroid

hormone decreases with age and that postmenopausal women have lower levels of active vitamin D than younger ones. Now, estrogen administration has been shown to increase the level of free, active vitamin D. A distinct abnormality in parathyroid secretory function and vitamin D action has been demonstrated in osteoporosis.

Discovery of the Cystic Fibrosis (CF) Gene. Using refined restriction enzyme methods and genetic probes in the region of the CF gene, investigators were able to map the position of each length fragment

Examination of the Intestinal Wall by Endoscopic Ultrasound Probe. With a specially designed echo probe in the tip of a fiber optic endoscope, it is now possible to view lesions beneath the mucosal lining, determine the depth of invasion of the intestinal wall, and visualize cross-sectional anatomy by means of high-frequency, high-resolution, real-time ultrasound images.

Gastritis and Peptic Ulcers. The spiral organism *Helicobacter* (formerly *Campylobacter*) *pylori* is found in the



In 1989, the cystic fibrosis gene was identified and characterized.

in its region of DNA. This approach was combined with the knowledge gained from screening DNA segments from a large chromosome 7 library to identify probes near the CF gene to narrow the candidate region to even shorter segments of DNA. Collaborating teams of researchers looked for segments of DNA that were expressed in epithelial tissue (as in CF), using RNA expressed in this type of tissue to screen segments of DNA from the region of the CF gene. Thus the gene was finally found. This work may allow improved screening for CF carriers and perinatal diagnosis; it illustrates the rewards of basic research.

stomach of many adults but is strongly associated with chronic active gastritis and peptic ulcer. Investigators supported by NIDDK have now shown that they can prevent virtually any recurrence of peptic ulcer disease by eradicating the *H. pylori* infection with antibiotics and bismuth compounds, which together have been effective in total healing of the ulcer.

Human Liver Transplantation. Developed with NIDDK support, the new University of Wisconsin organ perfusion solution has proved to be a major advance in liver transplantation, effectively doubling the period of time a donor liver can remain usable.

Primary Biliary Cirrhosis (PBC). Two mitochondrial antigens, identified by autoantibodies and found in 95 percent of patients with PBC, have now been purified, cloned, identified, and used to develop sensitive assays (ELISA assays) for the rapid detection of antimitochondrial antibodies in PBC. The autoantigen can also be used to investigate cellular immunity and T cell reactions in PBC.

Gallstones. Administration of the bile salt ursodeoxycholic acid has been shown to be effective in a group of patients at risk of developing stones because of rapid weight loss regimens or of recurrence of gallstones following removal. Other therapeutic techniques for gallstones now include ultrasonic lithotripsy and direct infusion of methyl-tertiary butyl ether to dissolve cholesterol gallstones. A new approach to elimination of noncholesterol components of gallstones uses EDTA-detergent-N-acetylcysteine solutions.

Relationships of Body Composition to Energy Expenditure. New NIDDK-supported research shows that, among groups matched for *weight*, fatter individuals have reduced energy expenditure and capacity for thermogenesis (heat generated with food intake). Among groups matched on *lean body mass*, the fatter subjects have diminished thermogenesis but not reduced resting energy expenditure. Body composition (percent body fat and total body fat mass), rather than body weight itself, is associated with increased cardiovascular disease risk. This work may suggest ways to improve the prevention and treatment of obesity.

Major Renal Function Alterations After Immune-Induced Glomerular Injury. Important glomerular functional alterations can now be followed throughout the clinical course of immune induced injury, allowing frequent assessment of the need for and effectiveness of therapy in immune-related diseases of the kidney.

Benign Prostatic Hyperplasia (BPH). NIDDK-supported researchers have shown there are high concentrations of basic fibroblast growth factor in the adult prostate gland in hyperplastic regions, whereas the levels in normal tissue are low. In addition, specific growth factors from the testes are secreted in the semen. Testis-derived growth factor may have a direct role in the initiation or stimulation of BPH.

Impotence in Men With Diabetes Mellitus. There is an impairment of penile vascular smooth-muscle relaxation (autonomic nerve mediated) in diabetic men; relaxation of this smooth muscle allows blood to enter the penis and cause an erection. The degree of impairment increases with the duration of diabetes. Another potential cause of impotence in diabetes is a low level of the substance endothelin, which is produced by normal blood vessels. The vascular abnormalities are not due to smoking and hypertension. These studies of impairment of autonomic control in diabetes provide a scientific basis for treating impotence by injection of smooth-muscle relaxant and vasodilator substances such as papaverine.

Interstitial Cystitis (IC). NIDDK-supported researchers have made progress in understanding the most common symptoms of IC (pain and urinary urgency and frequency) using NIDDK-established diagnostic criteria. It was found that urea (a small molecule present in normal urine) was able to "leak" through the bladder lining in IC patients, causing severe symptoms not seen in normal control subjects. Glycosaminoglycans normally form a protective layer on the surface of the bladder epithelium. Protamine sulfate, a compound that neutralizes the protective layer, allowed urea to cross this layer and enter the bladder muscle layer, causing pain and urinary frequency in normal volunteers. Both the leakage and the symptoms could be reversed by another substance,

heparin sulfate, which is known to restore the altered glycosaminoglycan layer. In a pilot study of some IC patients, instillation of heparin sulfate served to prevent both the leakage and the urea-induced symptoms.

Vitamin B_{12} Deficiency Without Anemia in Neuropsychiatric Patients. A sensitive new assay has been developed using capillary gas chromatography with mass spectrometry for detecting and quantifying urinary substances observed in cases of vitamin B_{12} or folate deficiency. In studies of patients with clinically important B_{12} deficiency without concurrent anemia, investigators have identified a subgroup of individuals who have neuropsychological disorders because of the B_{12} deficiency. Reversal of these disorders was possible using vitamin B_{12}.

Acquired Immunodeficiency Syndrome (AIDS). A retrospective study of bone marrow biopsy specimens of patients with acquired immunodeficiency syndrome (AIDS) has shown an unusually large number of denuded nuclei in the large platelet-containing megakaryocyte blood cells in all AIDS marrows examined, a finding unrelated to the peripheral blood platelet count. The presence of human immunodeficiency virus (HIV) gene sequences in megakaryocytes has been confirmed (by hybridization with an HIV-RNA probe tagged with a tracer). These findings provide one explanation of the thrombocytopenia seen in HIV infection.

Hematopoietic Growth Factor Therapy. For the correction of neutropenia, several hematopoietic growth factors, including granulocyte-colony stimulating factor (G-CSF), have now been cloned and produced by recombinant DNA techniques. Clinical trials now in progress show significantly fewer side effects (fever, bone pain, oral ulcers) with G-CSF than with a related growth factor, granulocyte-macrophage CSF. This finding raises the possibility that G-CSF may have many other clinical applications.

Future Opportunities

Advances in basic knowledge are continually and productively expanded into clinical and population-based studies and trials and into programs of technology transfer and information dissemination to the biomedical research community, practicing physicians, and the public. Programs of Institute-wide emphasis will include minority health issues, analysis and planning related to national population surveys and to epidemiology research, trans-NIH programs such as AIDS research and the mapping of the human genome, and the new forms and directions of NIH collaboration with industrial research and development teams.

National Institute of Environmental Health Sciences

Director's Preface

Almost three decades ago, Rachel Carson's book *Silent Spring* alerted the public to the threat of pesticides and ushered in the first modern age of the environment, changing forever America's environmental landscape and laying the foundation of our existing laws and programs intended to protect health and the environment.

Today, reports of dying wildlife in poisoned reservoirs and estuaries; sewage washing ashore on popular beaches; contaminated drinking water from agricultural fields, toxic dumps and industrial site runoff; air increasingly polluted by emissions from growing numbers of cars, trucks, and industrial plants; and grim descriptions of life on a "greenhouse" earth are again raising the world's awareness of the environment and its potential effects on human health.

Science is demonstrating that our planet is more vulnerable than had previously been thought; activities of modern industrial societies can alter fragile natural balances of the global environment that are not necessarily self-correcting. To our regret, we are learning that local activities can have global impacts. Dangers can develop over long periods, causing effects that are not easily reversed. There is potential for large and relatively sudden, rather than incremental, change. Plausible consequences are grave, yet cannot be predicted with certainty. We can no longer pretend that nothing is happening, or that the planet will somehow automatically adjust to the billions of tons of pollutants to which it is being subjected. The consequences for our world reinforce the need to answer complex questions about the relationship between our environment and ourselves—questions that require an adequate science base to produce valid answers.

Major Accomplishments

Progress being made in understanding and combating environmental health problems is, to a significant degree, a direct result of the longstanding commitment of scientific expertise and research resources by the National Institute of Environmental Health Sciences (NIEHS). Among its major accomplishments are the following:

- Developing the largest available data base on the human health effects of exposure to ambient and indoor air pollutants and acid aerosols. This data base has been the basis on which many of this country's clean air standards have been and continue to be formulated.
- Supporting landmark epidemiological studies reporting lung tumors and mesothelioma in asbestos workers and their family members, and establishing that cigarette smoking greatly increases the risk of cancer in asbestos-exposed workers.
- Developing a laboratory animal model that confirmed that DES (diethylstilbestrol) exposure during pregnancy was responsible for vaginal cancer in female offspring; alerting physicians to potential problems in males exposed *in utero*.

- Determining that prenatal lead exposure at levels previously thought "safe" is associated with developmental delays, preterm delivery, and low infant birth weight.
- Discovering that the activation of certain oncogenes (cancer-causing genes) is unique to tumors induced by specific chemicals.
- Completing extensive toxicologic evaluation in long-term rodent studies, including report publication, for approximately 350 chemicals. Under the conditions of these studies it has been determined that such substances as the food-borne fungal toxin ochratoxin A, and the industrial chemicals benzene and 1,3-butadiene are potent carcinogens. Such animal studies have also provided a reasonable degree of certainty that many chemicals, including penicillin VK, erythromycin stearate, and the high-volume industrial chemical toluene, are not likely to be carcinogenic in humans.
- Performing the most extensive evaluation ever done on the predictive utility of the Ames mutagenicity assay; determining that although a high proportion of mutagens are carcinogens, a number of mutagens are not, and that there appear to be nonmutagenic carcinogens missed by this testing screen.
- Maintaining, for over two decades, the Nation's only continuous research training grants program in the environmental health sciences. Graduate and post-graduate students supported by this program staff environmental toxicology and biomedical research laboratories in industry, government, and academia.
- Characterizing in detail the toxicity and mechanism of action of the polychlorinated biphenyls (used in electrical transformers) and polybrominated biphenyls (flame retardants).

Continuing Challenges

Global Warming and Human Health Effects. In addition to possible effects on agriculture, forestry, and water resources, it is clear that global climate change could have a range of both primary and secondary effects on human health. Direct effects include potential reproductive problems and other consequences of heat stress. Indirect effects may include changes in habitats of insects that carry disease. For example, mosquito- or tick-borne diseases and some encephalidites might increase in now-temperate areas.

Intensified development of alternatives to fossil fuels will require more complete understanding of the potential health effects associated with the alternatives.

Human Health Effects Related to Ozone Depletion. The ozone layer in the stratosphere, 6 to 30 miles above the earth's surface, is essential to life on earth. It absorbs from the sun radiation that is damaging to animal and plant cell structure, and distribution of ozone through the upper atmosphere has major implications for global climate. In 1974, it was suggested that damage to the ozone layer from release of chlorine into the atmosphere could unleash a process that would continually destroy ozone for decades. A single chlorine atom is capable of eliminating tens of thousands of ozone molecules.

Chlorofluorocarbons (CFC's), which break down in the stratosphere to release chlorine, nearly doubled in the atmosphere between 1975 and 1985, even though production had begun to level off in the same period. CFC's vaporize at low temperatures, making them perfect as coolants in refrigerators and air conditioners, as propellant gases in spray cans, and as blowing agents used in the manufacture of plastic foam materials. They are inexpensive to manufacture and are not known to be toxic. CFC's do not break down quickly in the lower atmosphere, but rather they migrate slowly

upward, to be broken down by atmospheric radiation in the stratosphere. Even if CFC uses were curtailed and their emissions were to level off or decline, they would continue to accumulate in the stratosphere for decades.

The Environmental Protection Agency estimates that reductions in stratospheric ozone may allow sufficient additional ultraviolet radiation to reach the earth's surface to cause more than 150 million new cases of skin cancer in the United States, by the year 2075, resulting in more than 3 million deaths. Other possible effects include eye cataracts, damage to the human immune system, serious impacts on agriculture and fisheries, increased urban smog, and global climate warming.

NIEHS-supported scientists are looking at how ultraviolet radiation damages DNA (the human hereditary map) and how skin cells repair the damage. Understanding the mechanism of injury could help in finding ways to block and repair ultraviolet damage. Substitutes for CFC's are being developed. NIEHS is concerned about the human health consequences of proposed replacements; NIEHS toxicological studies of two of them indicated that the compounds cause cancer in laboratory animal models. These findings suggest that more information on potential health effects is needed before those compounds are widely used.

Lead Absorption in Children and Other Populations. Recent research findings among children indicate that low-level lead poisoning can lower IQ scores and cause delayed mental development, hearing dysfunction, and other grave health effects that persist through adolescence and beyond. There is additional evidence of the harmful consequences of exposure to very low levels of lead by way of maternal exposure to the fetus. Failure to act on what we now know will consign our children, and ourselves, to a future deprived of full realization of our potential as a society. There are 5 to 6 million deteriorating housing units with lead-shedding paint in the United States, which threaten an estimated 2 million young children. NIEHS has long supported scientists who are pursuing effective, safe treatment to lower body-lead burdens from lead exposures and looking for ways to lessen exposure. NIEHS scientists also have begun to explore the effects of lead in aging populations. They are looking at increased susceptibility to lead's effects as metabolism changes and the lead stored in bone is released, particularly in postmenopausal women with osteoporosis.

Effects of Acid Aerosols and Other Air Pollutants on Lung Function. Increased use of fossil fuels is linked to possible global warming and has raised important questions about the health effects of acid aerosols that form from burning these fuels. Concerns range from worry that short-term exposures to sulfur oxides may cause asthma attacks, to the supposition that microscopic acidic aerosol particles may directly damage people's lungs. There is also speculation that deposition of acid rain leaches toxic metals from soils, water pipes, and other sources into drinking water and may be linked to a range of maladies including lead poisoning and Alzheimer's disease.

NIEHS supports studies to relate human health effects and actual measurements of acidic aerosol pollutants in acid rain. Such information may provide the basis for developing preventive and therapeutic strategies. For example, research at New York University has shown that ozone at ground level, produced when gasoline vapors and emissions from burning fossil fuel interact with sunlight, is associated with effects on lung function ranging from asthma attacks to increased risk of respiratory illness. More important, studies with exercising adults and healthy children found decreased lung function as ozone and related air pollutants increased, although the ozone levels were within existing ambient air quality

standards. These effects were greater in pollutant mixtures than could be explained by simply adding the separate effects seen in laboratory studies of individual pollutants. Other researchers are now confirming the potential interactive effects of the acid aerosols with oxidant gases.

Kidney Disease and Over-the-Counter Pain Medications. The United States Government spends more than $3 billion each year on dialysis and for patients with end-stage kidney disease. There is currently no cure for kidney failure. It is therefore crucial that preventable causes of kidney disease be identified. NIEHS scientists recently completed the first phases of a study designed to evaluate the contribution of environmental factors to kidney disease. The study explored the risks associated with medications and occupational exposures to solvents and other chemicals, and the possibility of links to other diseases such as diabetes and hypertension. NIEHS scientists found that daily use of pain-relieving drugs containing phenacetin or acetaminophen sold over the counter is associated with chronic kidney failure. Phenacetin was removed from most pain medications in the late 1970's because of reports linking the drug with kidney cancer, but medications that once contained phenacetin now contain acetaminophen, a chemically similar drug that is used in many popular aspirin-free pain medicines. Acetaminophen usage has increased dramatically in the past 10 years or so. The NIEHS study suggests that heavy use of this drug should be carefully monitored and that daily use for long periods of time should be avoided.

Confirming Mechanisms of Chemically Induced Cancer. NIEHS is developing sensitive tests to detect activated oncogenes in chemically induced and naturally occurring rodent and human cancer. Oncogenes are primal genetic agents (segments of DNA) that can set the growth of a cancer in motion when changed or activated in various ways. Important findings are emerging from this work. For example, a study of human lung tumors detected a much higher percentage (85 percent) of activated oncogenes than had previously been reported in the literature. Such findings affirm the utility of this laboratory system for determining which chemicals pose significant risk of causing cancer, and they have potentially profound implications for cancer prevention and therapy.

Identifying Cancer-Causing Chemicals. Rodents have long been used in experimental drug testing and safety trials for new chemicals, but now the role of the mouse as a human surrogate could be dramatically changed. Scientists have begun to breed strains of rodents called transgenic mice, which have genetic characteristics tailored for specific biomedical research purposes. NIEHS scientists are working with other NIH components to develop a mouse strain that will give the model special susceptibility to tumor formation.

Potential uses for transgenic animals are extraordinary. For example, NIEHS is attempting to identify potentially dangerous chemicals known as mutagens, which cause alterations that disable essential genes or change their message into something harmful. For example, such changes often turn normal genes into oncogenes. At present, chemicals are evaluated for their ability to cause mutations by applying them to dishes of bacteria that grow only if a mutation occurs. Bacterial assays detect only a portion of dangerous chemicals and they cannot distinguish among mutations that might cause cancer in humans and those that might be harmless. Many compounds do not become carcinogenic until they are actually processed through a mammal. NIEHS has inserted a gene with a specific, identifiable characteristic into a mouse. This model has the potential to speed the identification of cancer-causing chemicals, taking months instead of years.

National Eye Institute

Director's Preface

Diseases of the eye and visual system cause suffering, disability, and loss of productivity for millions of people. In economic terms, eye diseases and blindness cost the Nation about $16 billion annually.

Significant progress against blinding and disabling eye and vision disorders has been made since 1968 when the National Eye Institute (NEI) was created. During the past 2 years, NEI-supported scientists have reported findings that substantially further that progress. But with each advance come more questions that must be answered if the complexities of vision are to be fully understood and the means of preventing and treating visual system diseases are to be found.

The time is ripe with opportunity for advancing knowledge of the visual system. Not only has vision research matured and diversified, but revolutionary developments in scientific technologies also have occurred, which make possible studies undreamed of only a few years ago. Increasingly, the most advanced techniques in the biological sciences are being applied to understand the visual system and the disorders that affect it. Virtually every major area of this field has been revitalized by these dynamic sciences, including molecular genetics, immunology, and cell biology, and it is clear that they will provide the key to further achievements in the coming years.

To highlight particularly the achievements and opportunities in the neurosciences, the President and Congress have designated the 1990's as the "Decade of the Brain," and NEI enthusiastically supports the high priority that neuroscience research has been accorded by this action. NEI currently supports more than $80 million in basic and clinical neuroscience. With approximately 38 percent of all fibers entering or leaving the central nervous system by way of the optic nerve, the visual system provides unique opportunities for studies that not only bear on vision but also are generalizable to all of neuroscience.

Program Accomplishments and Opportunities

Retinoblastoma. As reported in the 1987-88 biennial report, retinoblastoma (RB), a sight- and life-threatening eye cancer that occurs in children, has been found to be associated with loss or alteration of the RB gene. The normal function of the RB gene, it is believed, is to suppress tumor formation. In recent experiments designed to test this hypothesis, scientists demonstrated that introduction of a cloned RB gene into cultured RB cells significantly inhibited cell growth and suppressed tumorigenesis in mice. In studies of RB gene expression and replacement in other types of tumor cells, scientists have shown that RB gene replacement modifies the cancerous properties of both osteosarcoma and prostate cancer cells. These studies point to the possible utility of gene therapy in treating some types of cancer.

Although molecular genetics research has pinpointed the cause of RB, a major

obstacle has been the lack of an animal model for this disease. Now, however, NEI grantees have developed a line of mice with inherited eye cancers that closely resemble the human RB in cell type, structure, and biochemistry. This new model provides scientists with the opportunity to study the process of malignant transformation in RB. It also should prove valuable for developing and testing drugs to treat RB.

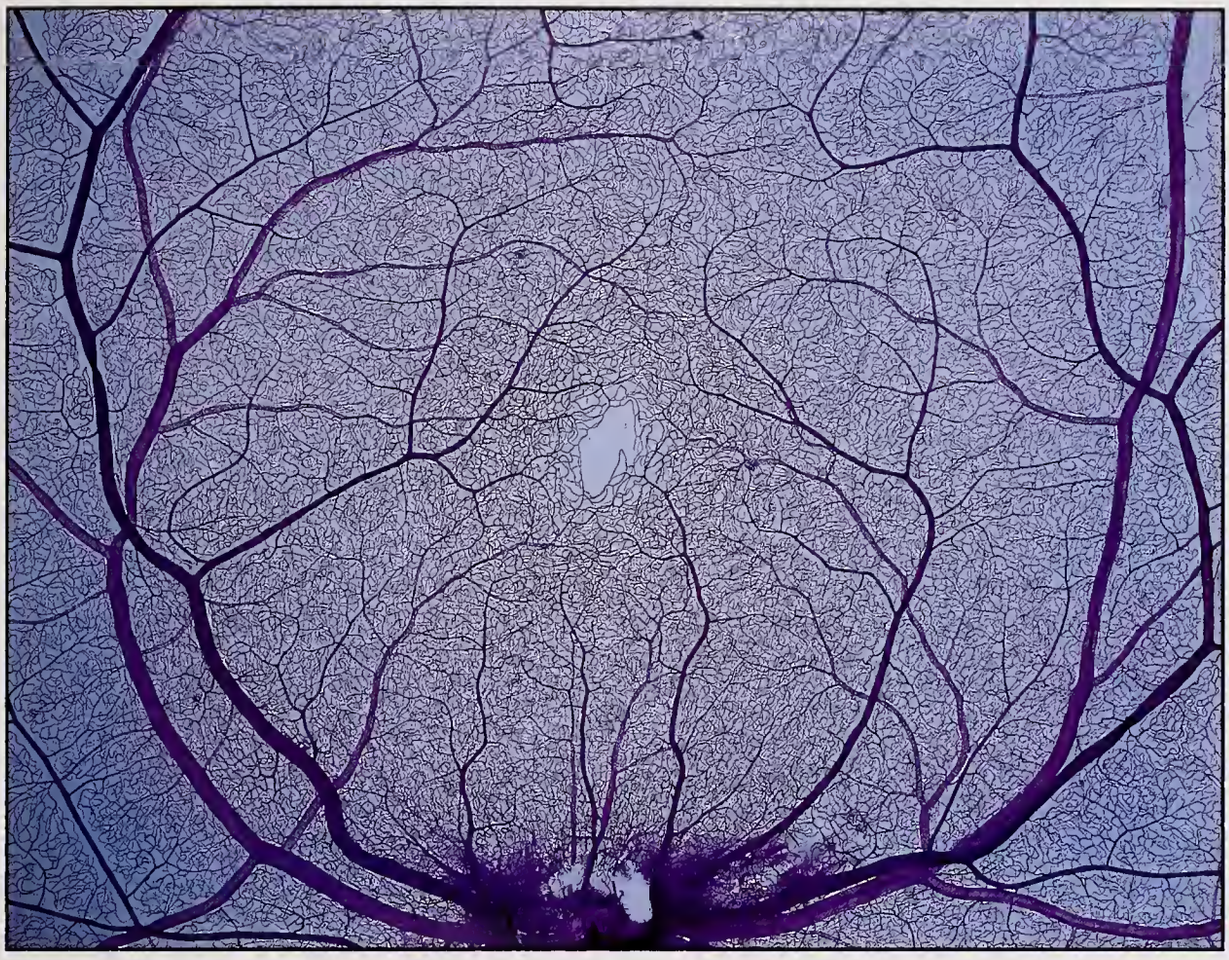
Retinitis Pigmentosa (RP). RP is a group of inherited retinal degenerative diseases characterized by a progressive loss of vision due to the degeneration of the retina's photoreceptor cells. Recently, the gene for autosomal dominant retinitis pigmentosa (ADRP), a type of RP that is inherited if either parent has the gene, was localized to chromosome 3. That chromosome is known also to contain the gene for rhodopsin, the light-sensing pigment found in photoreceptor cells. Building on this work, other NEI-supported scientists studied the rhodopsin gene of patients with ADRP and discovered a mutation in the gene of patients with one form of ADRP. No other gene defect has been described for any form of RP. Investigators are now trying to determine how this rhodopsin gene defect leads to the degeneration of photoreceptor cells.

In other RP-related studies, including the retinal pigment epithelial cell transplants described in the "Advances and Opportunities in Biomedical Research" section of this report, investigators have successfully transplanted normal photoreceptor cells from newborn rats into the light-damaged retinas of albino rats. The transplanted photoreceptors survived the surgical procedure for extended periods and appeared to be metabolically active. Although there is much research to be done before such transplantation can be attempted in humans, these results demonstrate the potential ability of transplanted healthy cells to replace damaged or degenerating retinal cells such as those seen in RP.

Molecular Biology of Color Vision. Years of pioneering research to identify visual pigment genes in both cone and rod photoreceptor cells have provided the foundation for applying molecular biological techniques to the study of inherited color vision deficiency in humans. Research conducted on 12 families affected with blue cone monochromacy (a rare, X-linked, inherited disorder of color vision) has shown that a specific region of the DNA coding for the red and green visual pigments is missing in these patients. Thus, the molecular basis of blue cone monochromacy has now been identified. This study confirms that inherited variations in human color vision are caused by alterations in the genes that encode the visual pigments, and it serves as a guide for studies of other inherited human color vision defects.

Uveitis. Uveitis (inflammation of the inner eye) causes about 10 percent of the cases of severe visual impairment in the United States. Earlier research studies led to the discovery of a uveitis-promoting antigen and development of an animal model for this devastating disease. Recently, scientists have been able to prevent experimentally induced uveitis by feeding the animal the antigenic protein that induces the destructive immune response. The antigen induces T cells of the immune system to suppress the uveitis. Plans are now under way to begin oral administration of this antigen to uveitis patients. This research offers the possibility of providing a new therapeutic approach to the management of chronic, autoimmune uveitis that may be less toxic than the immunosuppressive drugs now used to treat this disease.

Accommodation and Myopia. Animal models of myopia are now beginning to clarify the relationship between accommodation and the development of myopia (nearsightedness), a condition that affects 25 to 30 percent of the American population. Accommodation is



The human retinal vasculature. The clear zone (center) is the avascular portion of the macula, the part of the retina that is responsible for sharp central vision. In diabetes, fluid may leak from blood vessels and cause sight-threatening macular edema (swelling). The Early Treatment Diabetic Retinopathy Study (ETDRS) showed that focal photocoagulation in eyes with clinically significant diabetic macular edema substantially reduces the risk of visual loss.

the process by which the refractive power of the eye's lens increases (the lens assumes a more spherical shape and thickens in its center) so that the image of a near object will be focused clearly on the retina. Researchers trained monkeys to perform a complex letter discrimination task at close distances for 2 to 3 hours per day. One eye was then treated with atropine (a drug commonly used to dilate the pupil during eye examinations) so that it temporarily could not focus on the target. The untreated eyes of three of the four monkeys in the experiment became more myopic because they grew in axial length. This finding suggests that axial growth is stimulated when the animal is required to accommodate for a substantial part of each day. There has been considerable clinical interest in this research because of the possibility (as yet unproved) that intensive near work early in childhood may lead to myopia.

Glaucoma Treatment. The Fluorouracil Filtering Surgery Study is a multicenter, randomized clinical trial that was designed to determine whether postoperative injections of 5-fluorouracil (5-FU) under the conjunctiva (the delicate membrane that covers the exposed surface of the eye) would increase the success rate of glaucoma filtering surgery in patients with a poor prognosis. Filtering surgery (the creation of a drainage channel to allow fluid to leave the eye and thereby relieve the buildup of intraocular pressure that occurs in glaucoma) is standard treatment to prevent blindness

from glaucoma that cannot be controlled by medication. The study tested the effectiveness of 5-FU in preventing formation of the scar tissue that sometimes blocks the channel created by the filtering surgery. One year after surgery, only 27 percent of the patients who had received 5-FU needed another operation compared to 50 percent of those who had had surgery alone. Results also show that 66 percent of the patients receiving 5-FU maintained satisfactory intraocular pressure without medication, compared to only 36 percent of those who did not receive 5-FU; further, of the patients needing medication, those in the 5-FU group needed lower doses and fewer types of drugs than those who had surgery alone. Study investigators will continue to follow patients to evaluate the long-term safety of 5-FU in high-risk glaucoma patients.

Epidemiology of Visual System Diseases. It is known that certain eye diseases are related to the aging process, but until recently there had been no accurate, up-to-date information about the prevalence of blindness and visual impairment among older people. The Baltimore Eye Survey was designed to provide this information by studying a large, multiracial population that could serve as a model for many urban areas in the United States. The participants in the population-based sample of 5,300 blacks and whites aged 40 or older received an ophthalmologic screening examination that included detailed visual acuity measurements. The survey found that the prevalence of blindness and visual impairment in blacks was double that of whites. The rates of vision loss for both groups rose dramatically with age, but there was no difference between males and females in the rise. From this sample, the researchers estimate that more than 3 million Americans aged 40 or older are visually impaired and 890,000 of these are bilaterally blind.

Investigators also found to their surprise that the vision of more than 50 percent of the subjects could be improved by refractive correction, in some cases by three or more lines on the eye chart. This finding underscores the importance of eye health education to encourage periodic comprehensive eye and vision examinations and suggests the need for programs to improve access to basic eye care services in inner-city populations.

Age-related macular degeneration (ARMD) is the leading cause of severe visual loss among people aged 60 and older. To ascertain risk factors for ARMD, NEI is funding the Age-Related Eye Diseases Study, which will enroll 4,000 patients at 10 participating clinical centers. Baseline data from this natural history study will be important in designing future clinical trials for the prevention or treatment of ARMD.

National Eye Health Education Program (NEHEP). Considerable progress has been made in the development of NEHEP. A national program planning conference was held in early 1989, and several of the conference recommendations have been implemented, including establishment of a two-tiered advisory structure, a small planning committee and the NEHEP Partnership, comprising leading national organizations concerned with eye health; development of a research plan to assess the knowledge, attitudes, and practices of specific target audiences regarding eye health and eye disease; and establishment of an eye health education subfile on the Public Health Service Combined Health Information Database. Other recommended activities, such as establishment of a national, toll-free telephone information service, are under development.

Policy Issues

NEI recognized long ago that research needs and opportunities often far outnumber available funds and manpower and embraced formal program planning for setting research and program priorities. In 1989 NEI, in concert with the

Vision Research Program Planning Subcommittee of the National Advisory Eye Council (NAEC), began developing its next long-range national plan for vision research. Continuing in the tradition of involving the vision research community in the planning process, a number of expert panels have been established to advise NEI and NAEC in this effort.

Policy issues will be a major theme of this plan, and NEI has undertaken several innovative steps to involve the vision community in identifying and discussing the issues. In August 1989, NEI and NAEC held a policy planning forum, a first-of-its-kind public meeting between the Institute and vision research groups, which was dedicated solely to policy and administrative issues. Representatives of nearly 20 organizations that support vision-related research or represent people with visual diseases and disorders presented their organizations' views on policy issues and priorities. A followup meeting was held in April 1990 for expanded and more indepth discussion of selected topics, including research funding options and the adequacy and mix of current funding mechanisms; increasing costs of research grants; appropriate levels of support for research training and career development awards; ways to encourage greater participation of minorities in vision research; animal welfare issues; and scientific misconduct and conflict of interest. The subcommittee will prepare a report for inclusion in *Vision Research—A National Plan: 1992–1996*, which is scheduled for publication in March 1991.

National Institute of General Medical Sciences

Director's Preface

The National Institute of General Medical Sciences (NIGMS) supports research basic to the understanding of life processes—an understanding necessary for the eventual solution of specific disease-related problems. Often, studies initiated with NIGMS support go on to be funded by more disease-targeted institutes or agencies when the application of the work becomes apparent. In addition, basic research—such as the fundamental gene mapping and genome analysis studies originally supported by NIGMS and now funded by the National Center for Human Genome Research—may go on to become separate initiatives. Thus, the relatively untargeted biomedical research funded by NIGMS can lead in many directions.

One indication of the high quality and broad applicability of NIGMS-supported research is found in the numerous honors and awards given to Institute grantees each year. In 1989, the Nobel Prize in chemistry was shared by two long-time NIGMS grantees, Drs. Sidney Altman of Yale University and Thomas R. Cech of the University of Colorado at Boulder. The 1989 Lasker Award for basic medical research and the 1990 Passano Award, two of the most prestigious research awards given in this country, were won by Dr. Alfred G. Gilman of the University of Texas Southwestern Medical Center in Dallas. Dr. Gilman is a current grantee who is also a graduate of the NIGMS Pharmacology Research Associate (PRAT) Program.

In 1989, NIGMS significantly enlarged the scope of its minority research and research training support efforts when it assumed the administration of the Minority Biomedical Research Support (MBRS) Program from the NIH Division of Research Resources. The MBRS Program provides research grants to colleges, universities, and health professional schools with substantial minority enrollments. These grants support research by faculty members, strengthen the institutions' biomedical research capabilities, and provide opportunities for students to work as part of a research team.

In addition, NIGMS continues to support the highly successful Minority Access to Research Careers (MARC) Program, which helps minority institutions improve their science curriculums and funds research training for students and faculty members at these institutions.

NIGMS research activities are focused in four scientific areas: cellular and molecular basis of disease, genetics, biophysics and physiological sciences, and pharmacological sciences. Highlights of some recent accomplishments made by NIGMS grantees follow.

Research Programs

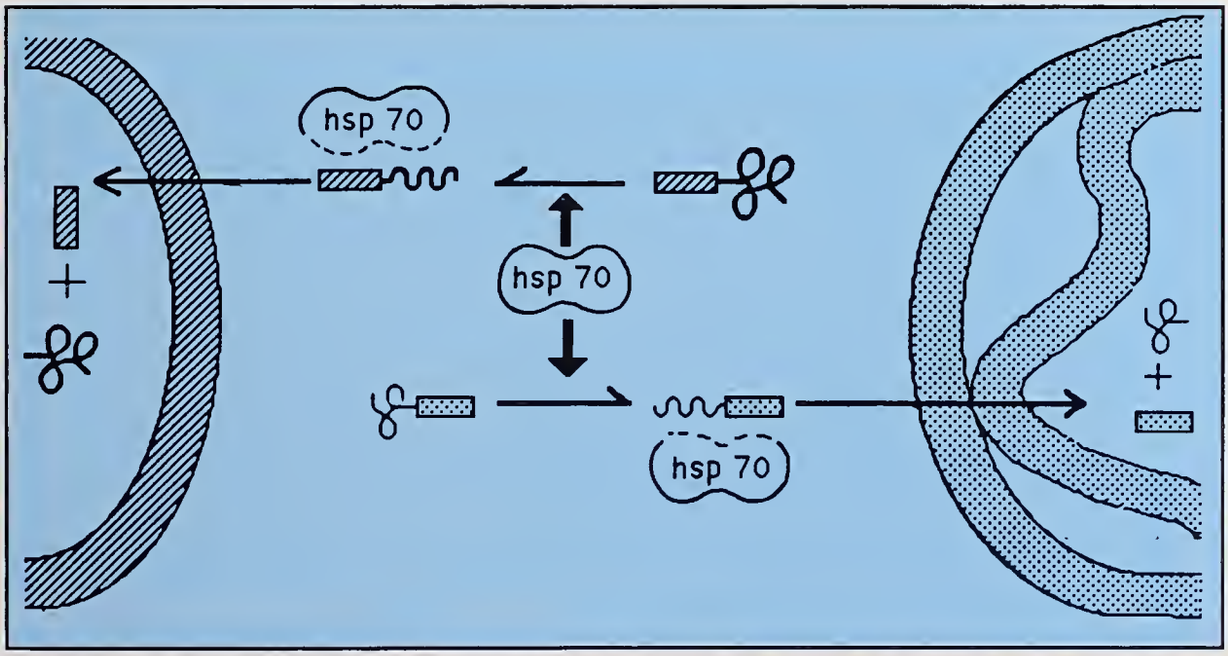
Cellular and Molecular Basis of Disease. Research supported by the Cellular and Molecular Basis of Disease Program contributes to the understanding of the structure and function of cells and cell components. This work is aimed at developing fundamental knowledge of life processes that will eventually lead to new ways to fight diseases.

Recently, NIGMS-supported scientists discovered a possible link between a protein called alpha-1 antichymotrypsin (ACT) and Alzheimer's disease. These investigators found that ACT is an integral part of the beta amyloid plaques present in the brains of people with Alzheimer's disease and that it is present in these plaques at high levels. Because ACT works elsewhere in the body to inhibit the activity of enzymes that break down other proteins, the researchers speculate that an excess of ACT might prevent brain enzymes from breaking down the plaque-forming beta amyloid protein. In this way, ACT—which should protect the brain from uncontrolled protein breakdown—may upset the delicate balance between enzymes and inhibitors and contribute to Alzheimer's disease.

Other NIGMS grantees, while studying the function of heat shock proteins (HSP's)—which are produced by virtually all organisms in response to environmental stress—have discovered that these proteins also play a role in the translocation of other proteins through cell membranes. HSP's apparently assist in unfolding these proteins before they are transported across membranes, and they also may aid in refolding proteins that have folded incorrectly. If these findings are confirmed, the study of HSP's may contribute to the commercial development of products applicable to a number of human disorders, because failure to synthesize proteins that fold properly is often a barrier to commercial production.

Genetics. Basic researchers supported by the NIGMS Genetics Program continue to make significant scientific discoveries leading to knowledge of the role that genetics plays in many diseases. Particular progress is being made in understanding the nature and function of genes that contribute to the development of cancer.

One group of researchers supported by NIGMS discovered an unexpected connection between cholesterol synthesis and the ability of an oncogenic (cancer-inducing) protein found in colorectal and pancreatic cancers to trigger cell division. This finding is the first to link cholesterol synthesis and the initiation of cancer. It not only helps scientists understand the processes that lead to cancer but also has



This diagram shows how some heat shock proteins (HSP's) may bind to other proteins to unfold them into a form that can pass through membranes. The HSP's dissociate with the protein when membrane penetration begins and can then work to unfold another protein.

prompted the idea that cholesterol-lowering drugs might find a place in the anticancer therapeutic arsenal.

Another NIGMS-supported researcher, who has been studying normal cell function for many years, is now advancing the fight against acquired immunodeficiency syndrome (AIDS). This researcher has provided insights into why the drug zidovudine (AZT) is toxic to normal cells. He discovered that AZT affects cell organelles called mitochondria, which are responsible for making the energy-containing compounds that cells must have to function. He has gone on to identify substances that act like AZT but appear to be less toxic to normal cells. These agents are currently being tested and may eventually lead to better therapies for AIDS.

Biophysics and Physiological Sciences. The Biophysics and Physiological Sciences Program supports studies that foster the development and application of physical principles to the study of biological problems, especially those of biological structure. Modern instrument development, particularly in the area of computers, has made possible careful, detailed structural analysis. Understanding the structure and function of molecules can lead to advances in the design of substances of therapeutic and industrial value. The program also funds research on biological responses to burn injury and other forms of trauma.

In 1989, a group of NIGMS grantees succeeded in using a new type of microscopy called scanning tunneling microscopy to obtain very good atomic-level images of DNA. This work is important because the binding of protein to DNA and other aspects of gene regulation depend on minute variations in the molecular structure of the DNA. Understanding this structure in relation to its activity may improve knowledge of the mechanisms of DNA interaction with such substances as cancer-causing agents or drugs and could thus have major implications for human health.

Another team of NIGMS grantees is developing a promising new method to improve burn wound closure. These researchers "seeded" connective tissue protein derived from cows with connective tissue cells from patients with extensive burn injuries. They then placed a layer of skin cells grown from a small sample of the patients' unburned skin on top of the seeded layer. This skin substitute is then grafted onto the burn wound. So far, the technique appears to reduce significantly the time between injury and satisfactory wound closure.

Pharmacological Sciences. Studies of synthetic chemicals and natural products that have biological effects, as well as the mechanisms of action of drugs and other chemical compounds in living creatures, form important areas of support in the Pharmacological Sciences Program. The Institute's substantial portfolio of basic research grants in chemistry is also administered in this program.

NIGMS-supported investigators have been studying the role of heredity in the metabolism of the drug propranolol in various populations, because it is known that sensitivity to this drug varies among racial groups. These researchers have found that propranolol, which is widely used to treat high blood pressure, is metabolized by two separate, genetically determined pathways, making it the only drug yet identified that is metabolized by two such systems. This discovery is of clinical significance because of the implications for adverse interactions between propranolol and other drugs. In addition, further study may yield some valuable information about the chemistry of the enzyme system involved in these metabolic pathways.

A group of NIGMS-supported scientists working in the area of basic chemistry has developed a family of more than 20 totally synthetic enzymes called "chemzymes,"

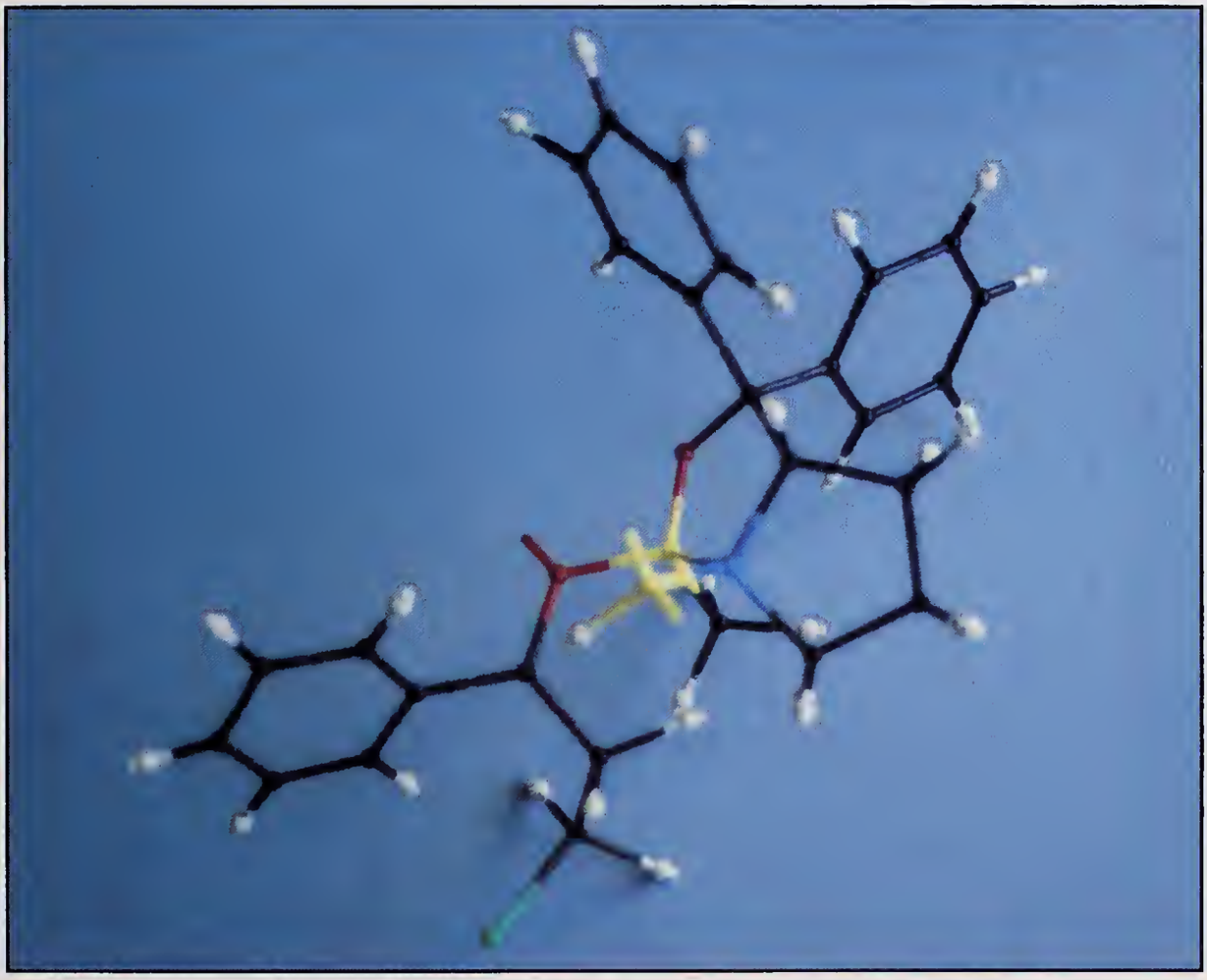
which are small molecules that catalyze certain reactions quickly and in such a way that only the biologically effective product is made. Moreover, chemzymes are produced by "rational" molecular design—that is, the scientists start out by understanding the chemical mechanisms involved in a particular reaction and then synthesize molecules with exactly the properties needed. This system provides much greater control over reactions, avoids the synthesis of unwanted byproducts, and should help scientists and pharmaceutical companies develop many compounds more quickly and less expensively than is now possible.

Research Training

The NIGMS-supported research training programs serve the research community by providing critically needed new scientists who have received broad, multidisciplinary training. NIGMS trainees often make significant contributions to the work of their laboratories and to the advancement of scientific knowledge. Many scientists who are now at the forefront of their fields received their training through NIGMS grants.

In addition to the training grants administered by NIGMS programs, the Institute has three special training programs: the MARC Program, the Medical Scientist Training Program (MSTP), and the PRAT Program.

The MARC Program supports research training of honors undergraduates in their third and fourth years of college, predoctoral students, and postdoctoral fellows. The MSTP, which was created to address



A model of a chemzyme taking part in a chemical reaction. This particular reaction can produce fluoxetine, a drug that may be useful in treating depression, chronic pain, and eating disorders.

NIGMS Minority Access to Research Careers (MARC) honors undergraduate students visit an NIH laboratory.

the shortage of clinical researchers, currently supports 735 M.D. and Ph.D. students at 29 institutions. The PRAT Program is a small intramural activity for which 10 or 11 recently trained scientists are selected each year for a 2-year period of postdoctoral research under the direction of senior researchers at NIH and the Alcohol, Drug Abuse, and Mental Health Administration.

The Future

The research supported by NIGMS in the past has had a profound effect on the progress of biomedical science. It is very probable that without this support for basic research, the present revolution in biology would not have occurred. The enormous scientific advances being made today are just beginning to yield new and better ways to treat, prevent, and cure disease. Further applications of the rapidly growing body of biomedical knowledge should make possible significant future improvements in human health.

National Heart, Lung, and Blood Institute

Director's Preface

The National Heart, Lung, and Blood Institute (NHLBI) provides leadership for a national program in diseases of the heart, blood vessels, lungs, and blood and in the uses of blood and the management of blood resources. Through research in its own laboratories and extramural grants and contracts, the Institute conducts a coordinated program that includes basic and clinical investigations, clinical trials, epidemiologic studies, demonstration and education projects, and research training and career development.

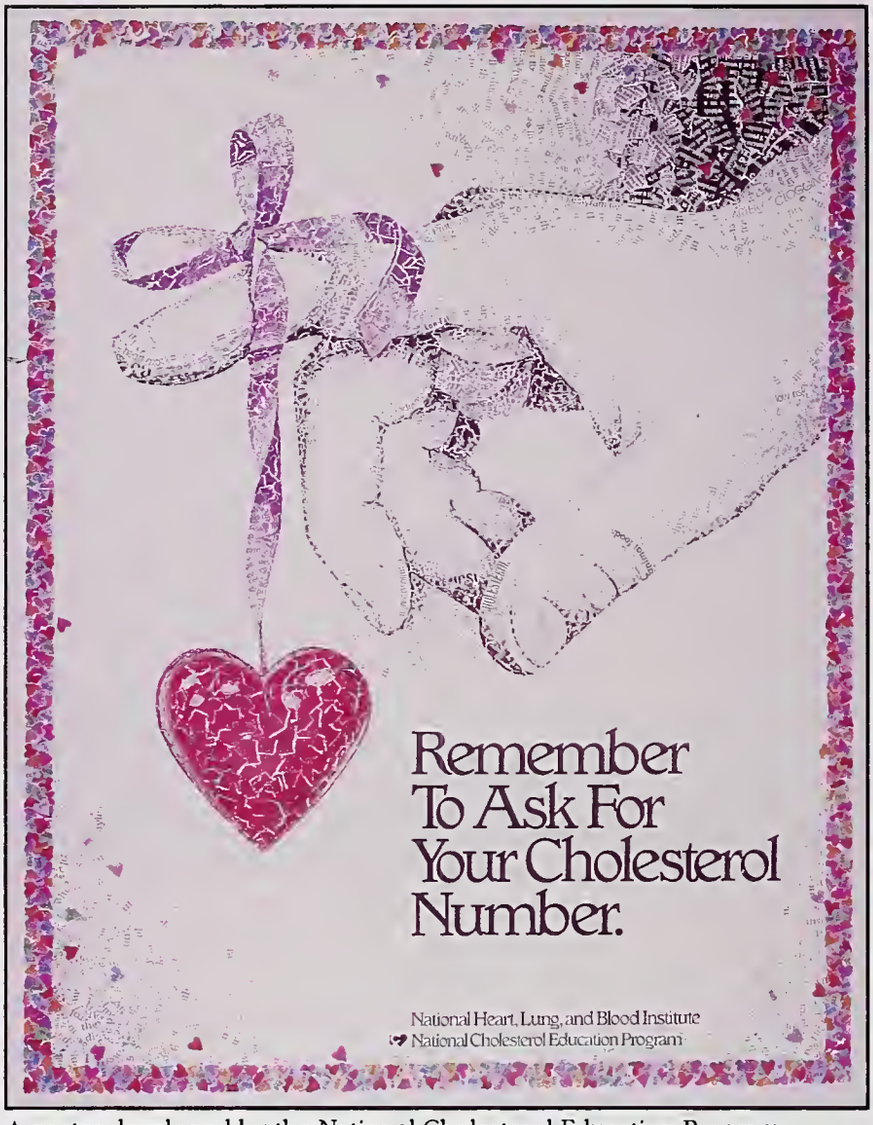
The search for new knowledge about normal states as well as pathologic processes has led to many notable achievements in diagnosis, treatment, and prevention that have in turn produced significant improvements in the public health of the United States. The highlights that follow exemplify the remarkable progress that can be realized when advances in basic sciences lead to clinical applications and clinical needs provide direction for new basic research.

Program Highlights

Cardiac Arrhythmia Suppression Trial. The Cardiac Arrhythmia Suppression Trial was designed to evaluate the potential effectiveness of three antiarrhythmic drugs in preventing sudden death in heart attack survivors who had mildly irregular heart rhythms. In April 1989, the use of two of the drugs, encainide and flecainide, was halted when it became apparent that death occurred almost twice as frequently among patients who took the drugs as among those who took a placebo. Physicians were immediately advised that these drugs should be used only by patients with life-threatening arrhythmias and not in the cases of mild arrhythmias for which the drugs had been widely prescribed. This experience underscores the importance of the clinical trial as a research tool in evaluating therapeutic applications.

Role of the Vascular Endothelium in Blood Pressure Control. For many years, the endothelial cells that line the blood vessels were thought to function solely as a wall to contain plasma proteins and present a blood-compatible surface. Basic science findings, however, have revealed that endothelial cells have a variety of functions. Recently, investigators identified endothelin, a protein secreted by endothelial cells that appears to play a significant role in the control of blood pressure. It is thought that endothelin produces increased arterial blood pressure by increasing coronary and peripheral resistance and decreasing cardiac output. These and other insights into the biology of the vessel wall offer the promise of future improvements in our ability to treat and prevent hypertension.

Hypertension in Blacks. Hypertension is a major risk factor for cardiovascular disease in black Americans. Mean blood pressure levels are higher in blacks than in whites, and more blacks than whites have hypertension. A series of investigations on biobehavioral factors in hypertension revealed that, under conditions of salt loading and stress, the cardiovascular



A poster developed by the National Cholesterol Education Program (NCEP) reminds patients to have their blood cholesterol level measured. The NCEP supports professional, patient, and public education to reduce the number of Americans with high blood cholesterol.

responses of hypertensive blacks are exaggerated, indicating increased peripheral vascular resistance. In addition, blacks score higher than whites on measures of hostility and anger expression—personality variables that other studies have found to be associated with risk of cardiovascular disease. Such advances in understanding the complex factors that produce a greater hypertension burden among black Americans are expected to lead to more effective approaches to reducing and preventing it.

Administration of Heart Attack Medication by Ambulance Paramedics. About 500,000 of the estimated 1,250,000 heart attacks that occur each year in the United States result in death, often as a result of ventricular fibrillation occurring between the onset of symptoms and the initiation of medical care. Recent clinical studies have shown that prompt administration of intravenous thrombolytic therapy can reduce this mortality by 20 to 50 percent. Phase 1 of an NHLBI-sponsored clinical trial evaluated methods to decrease delays in the administration of thrombolytic therapy. Results established the feasibility of having ambulance paramedics communicate by radio with hospital-based physicians to determine patient eligibility for thrombolytic therapy. Phase 2 will compare prehospital versus in-hospital administration of thrombolytic therapy with respect to mortality and preservation of myocardial function.

Regression of Atherosclerotic Lesions. New evidence has emerged that suggests that pharmacologic and lifestyle interventions can not only slow the build-up of atherosclerotic plaque in arteries, but also actually cause regression of existing lesions. A clinical investigation in which patients were given a combination of the drugs lovastatin, colestipol, and niacin to lower their cholesterol levels found lesion regressions in 35 percent of treated patients. Even more exciting are the results of a small study in which subjects adopted a program of severe dietary restriction, smoking cessation, relaxation training, and stress management. That study demonstrated that changes in diet and lifestyle alone can be highly effective in reversing blocked arteries.

New Approaches to Treating Cystic Fibrosis (CF). CF is the most common fatal inherited disease among white children. Heretofore, only palliative treatment has been available and most CF patients have died in young adulthood of pulmonary complications. Investigators are now studying a promising new therapy involving the use of an aerosolized form of the diuretic compound

amiloride that inhibits excessive salt and water absorption from CF secretions in the airway. Preliminary results obtained in adult patients indicate the ability of amiloride to normalize the flow properties of airways mucus and to slow loss of lung function in these patients. These findings, if confirmed, are expected to lead to a rapid effort to assess the protective effects of the drug in younger patients.

The recent discovery of the gene that causes CF offers new opportunities not only for identifying the basic biochemical defect underlying the disease but also for determining how it causes the characteristic pulmonary pathology. Based on this discovery, NHLBI-supported researchers are now pursuing the development of an animal model of CF. On another front, new techniques of cell culture have enabled production of "immortalized" CF cell lines capable of propagating indefinitely and faithfully expressing what appears to be a fundamental abnormality of airway epithelium in CF. The availability of this resource will facilitate studies of the pathophysiology of CF as well as design of therapies to correct the underlying metabolic error.

Neutrophil Abnormalities in Adult Respiratory Distress Syndrome (ARDS). ARDS affects approximately 150,000 persons annually and is among the more common fatal complications of surgery and major trauma. Life-threatening infections frequently accompany ARDS, and recent evidence suggests that an abnormality in neutrophils (cells that migrate to sites of infection) may contribute to the infectious process. Normal neutrophils alter their shape to pass through the relatively small pulmonary vessels and reach sites of infection and inflammation. However, neutrophils from ARDS patients appear to become trapped in the pulmonary capillaries, suggesting an impaired ability to modify their shape. By using pharmacologic agents that counteract the stiffening and retention of neutrophils, it may be possible to restore their ability to migrate to sites of inflammation and infection in patients with ARDS.

Effect of Smoking on Chronic Obstructive Pulmonary Disease (COPD). New research is providing clues to understand why some, but not all, smokers develop emphysema and other forms of COPD. The irreversible structural alveolar damage of emphysema is thought to result from an imbalance between elastase, which breaks down lung tissue, and alpha-1-antitrypsin, which inactivates elastase. Investigators recently reported that in some smokers large numbers of neutrophils accumulate in the capillaries of the lungs immediately after smoking. Because neutrophils are thought to be the main source of elastase, it is possible that some smokers suffer tissue destruction because of a localized excess of elastase released by accumulated neutrophils. Further research may show this condition to be a critical causative mechanism in the development of emphysema in smokers.

Asthma Education. NHLBI has been a leader in the development of asthma self-management strategies to improve patient function and reduce the frequency and severity of attacks and emergency room visits. Research results are now being widely disseminated through the National Asthma Education Program (NAEP), initiated in 1989 to provide patient, family, professional, and public education. The NAEP Expert Panel on Management of Asthma, whose report will be distributed in late 1990, is developing national guidelines for physicians who treat patients with asthma. NAEP will place particular emphasis on reaching members of minority groups who suffer disproportionately from asthma and on developing asthma education programs for schools. Such efforts will improve the quality of life for the millions of Americans who suffer from asthma.

New Therapeutic Strategy for Hemophilia A. Patients with hemophilia A lack factor VIII, essential for blood clotting,

and are treated with replacement transfusions of plasma-derived products. Up to 20 percent of repeatedly transfused patients, however, produce antibodies that inhibit factor VIII function. A therapeutic strategy to circumvent the presence of factor VIII inhibitors has been made possible by the development of recombinant factor VII, a clotting factor capable of bypassing the inhibitor effect. Purity, lack of infectious agents, and ease of administration make recombinant factor VII an attractive potential treatment not only for hemophilia A patients who have developed factor VIII inhibitors, but also for patients with other forms of the condition.

Transgenic Mouse Model for Human Hemoglobin. In an exciting development that opens new avenues for research on sickle cell anemia and other blood diseases, scientists have developed laboratory mice with blood cells that express human hemoglobin (the protein that carries oxygen throughout the body). Normal human hemoglobin genes were implanted into mouse embryos, and the embryos grew to adult mice that produce human hemoglobin. In addition, researchers have successfully implanted sickle hemoglobin genes into these animals to cause production of the human hemoglobin S found in patients with sickle cell anemia. These findings may lead to animal models of this disease for detailed studies and enhanced exploration of experimental treatments.

Pulmonary function testing can detect airways obstruction long before symptoms become apparent. The NHLBI Lung Health Study is investigating whether smoking cessation and bronchodilator therapy can slow the decline of pulmonary function and reduce the incidence of chronic obstructive pulmonary disease in smokers with early airways abnormalities.

Bone Marrow Transplantation. Bone marrow transplantation is an effective, accepted therapy for an increasing number of diseases of the bone marrow and the immune system. Until recently, most bone marrow donors were siblings carefully matched for human leukocyte antigen (HLA). However, it is now clear that good results can be obtained with marrow donated by matched community volunteers. The Institute's National Marrow Donor Program includes a National Bone Marrow Registry, which is a computerized file of individuals who have been HLA-typed and have agreed to participate as potential bone marrow donors. The number of listed donors has more than doubled in 1989 and is now near 100,000. More than 300 transplants have been performed using donors from the registry.

Gene Therapy. NHLBI intramural researchers have recently developed an innovative method of implanting cells that carry desired genetic information into animals. Organoids, or neo-organs, have been created that act as cell factories when implanted into animals. An organoid is produced by coating a three-dimensional plastic polymer with collagen and extracellular matrix molecules, then adding a growth factor to stimulate blood vessel growth. Cells that contain engineered genes are then transplanted onto this structure, and it is implanted into the animal and becomes part of its body. Although far from ready for use in humans, organoids have the potential to treat those genetic diseases that can be corrected by the secretion of a product, for example, clotting factor for hemophilia or insulin for diabetes.

Acquired Immunodeficiency Syndrome (AIDS). The NHLBI blood resources program supports research to develop more reliable methods of screening donated blood for human immunodeficiency virus (HIV). Recently, several promising new testing procedures have been developed that offer greater sensitivity, specificity, and technical convenience than those currently in use. Although blood-screening procedures are quite effective in preventing the transmission of HIV, researchers are also evaluating methods to inactivate viruses in donated blood. In recent studies, investigators have found that filters can remove leukocyte-associated virus, and chemical procedures can inactivate HIV isolates. These new methods are expected to increase further the safety of the national blood supply.

Clinical researchers have focused much attention on the lung, the organ most affected as a result of HIV infection. Scientists recently reported finding abnormally reduced levels of glutathione (a natural substance in the body necessary for immune function) in the lungs and blood of men infected with the AIDS virus. An aerosolized form of glutathione has been developed and is now being tested in humans to determine whether it can safely restore the deficiency in the lung. Because glutathione plays an important role in enabling the immune system to function normally, it is hoped that increasing the levels of glutathione will help prevent AIDS-associated lung infections.

National Institute of Neurological Disorders and Stroke

Director's Preface

The year 1990 is a major landmark in the history of the National Institute of Neurological Disorders and Stroke (NINDS). For four decades the Institute has supported neurological and neuromuscular research in institutions across the United States and around the world and conducted research in its own laboratories and clinics. We have made significant progress in understanding stroke, multiple sclerosis, epilepsy, Parkinson's disease, neurogenetic diseases such as lipid storage diseases and neurofibromatosis, muscular dystrophy, and brain and spinal cord injury. Further progress depends on a targeted but broad-based research effort uniting basic and clinical studies.

Congress and the President recognized the tremendous opportunities presented by research advances in the basic and clinical neurosciences, and the staggering human and social costs of disorders of the brain, by designating the 1990's the "Decade of the Brain." In this decade the causes of many disorders may well be identified; better treatments—perhaps cures—may be found. Learning about the brain and other elements of the nervous system—how they work to provide for learning, memory, performance, and how they fail when damaged by trauma, stroke, genetic disorders, and brain cell degeneration—is the objective of the research program of NINDS. The following are examples of the exciting recent research advances and the enormous opportunities that exist in the neurosciences.

Research Program

Parkinson's and Other Degenerative Diseases. In 1989, an NINDS-supported clinical trial revealed that treatment with the drug deprenyl delays the progression of symptoms in patients with early Parkinson's disease and postpones the need for L-dopa therapy. For the first time we have evidence of a drug that may slow the progression of a neurodegenerative disease. Deprenyl was also found to increase significantly the time patients remained gainfully employed, a benefit that will yield increased productivity and annual savings in health care costs of hundreds of millions of dollars. The findings are so striking that the trial was interrupted and modified to provide deprenyl to all patients in the continuing study. The trial will now determine the effect of long-term deprenyl treatment in association with L-dopa therapy, and the possible additional benefit of the antioxidant, vitamin E.

In other research, basic studies on neural tissue growth, animal studies addressing regeneration after implantation into a host brain, and studies on the effect of growth factors on regeneration and repair are progressing. Dopamine-producing cell grafts in particular are being studied in an effort to prolong their survival. Fetal animal brain tissue will survive implantation into an adult animal brain and grow for months, produce dopamine, and reverse parkinsonian effects. Studies have shown that similar results can be obtained in human patients. It also was found that placental cells

implanted in parkinsonian animals can reverse the syndrome.

The search for the Huntington's disease (HD) gene is continuing. A variety of high-resolution genetic and physical mapping techniques have narrowed the region for the HD gene to a small zone in the terminal end of the short arm of chromosome 4. Using new markers, the presymptomatic test for HD is now estimated as 99 percent accurate. Identifying and cloning the HD gene will lead to isolating its products and understanding the causes of the disease.

Finding genetic and biological markers for Alzheimer's disease (AD) will facilitate early, accurate diagnosis of the disorder. Genetic studies confirm that a location on chromosome 21 is linked to AD in a large number of families with an early-onset, dominantly inherited form of the disease.

The search for growth factors and other determinants of growth, development, and regeneration of axons should provide new potential approaches to therapy for degenerative diseases. Recently, through the use of growth factors and interleukin-1 in tissue cultures, our laboratories have characterized and localized the genetic material that produces the protein forming most of the amyloid plaques and neurofibrillary tangles in the aging brain. These studies could lead to control of amyloid precursor production as a prophylactic approach in AD and other dementias.

Recent animal studies of skin fibroblasts implanted into lesioned areas of brain may one day lead to treatment for people with central nervous system degeneration. Before implantation, scientists genetically modified the fibroblasts to secrete nerve growth factor. Animals with the modified implants had less nerve cell degeneration and even demonstrated enhanced sprouting of the axon portion of nerve cells. Although clinical applications require further study, these results are encouraging.

Enzyme-Replacement Therapy for Gaucher's Disease. Gaucher's disease is the most common genetic metabolic disease; some cases express severe neurological complications. It and other lysosomal storage diseases are caused by genetically determined enzyme deficits. Gaucher's patients in an NINDS enzyme replacement efficacy trial have had clearly demonstrable clinical benefit. Their anemia has been corrected, the size of their enlarged spleens and livers has decreased, and magnetic resonance

The remarkable results of enzyme replacement therapy for Gaucher's disease can be seen in these pictures of the same child before and after therapy. The enlarged abdomen before treatment is due to a swollen liver and spleen.

imaging indicates skeletal improvement. Continued research will establish dosage levels and evaluate long-term effects. In addition to refining this therapy, progress is being made in developing techniques that would permit transfer of the needed gene to bone marrow cells that could then be implanted in the patients; if successful, clinicians will have a method to treat Gaucher's disease that would be permanent and have few side effects.

Transplant Therapy for Muscular Dystrophy. One of the success stories in neuromuscular research is the discovery of the gene responsible for Duchenne's muscular dystrophy (DMD). Using the tools of molecular biology, scientists found the gene and its product, dystrophin, which is needed for normal muscle function. Normal embryonic muscle cells were injected into mice with a genetic defect analogous to DMD and became fused with the host cells; they produced the missing dystrophin. Studies are under way in humans to determine the feasibility of this use of "myoblast transfer" to treat muscular dystrophy.

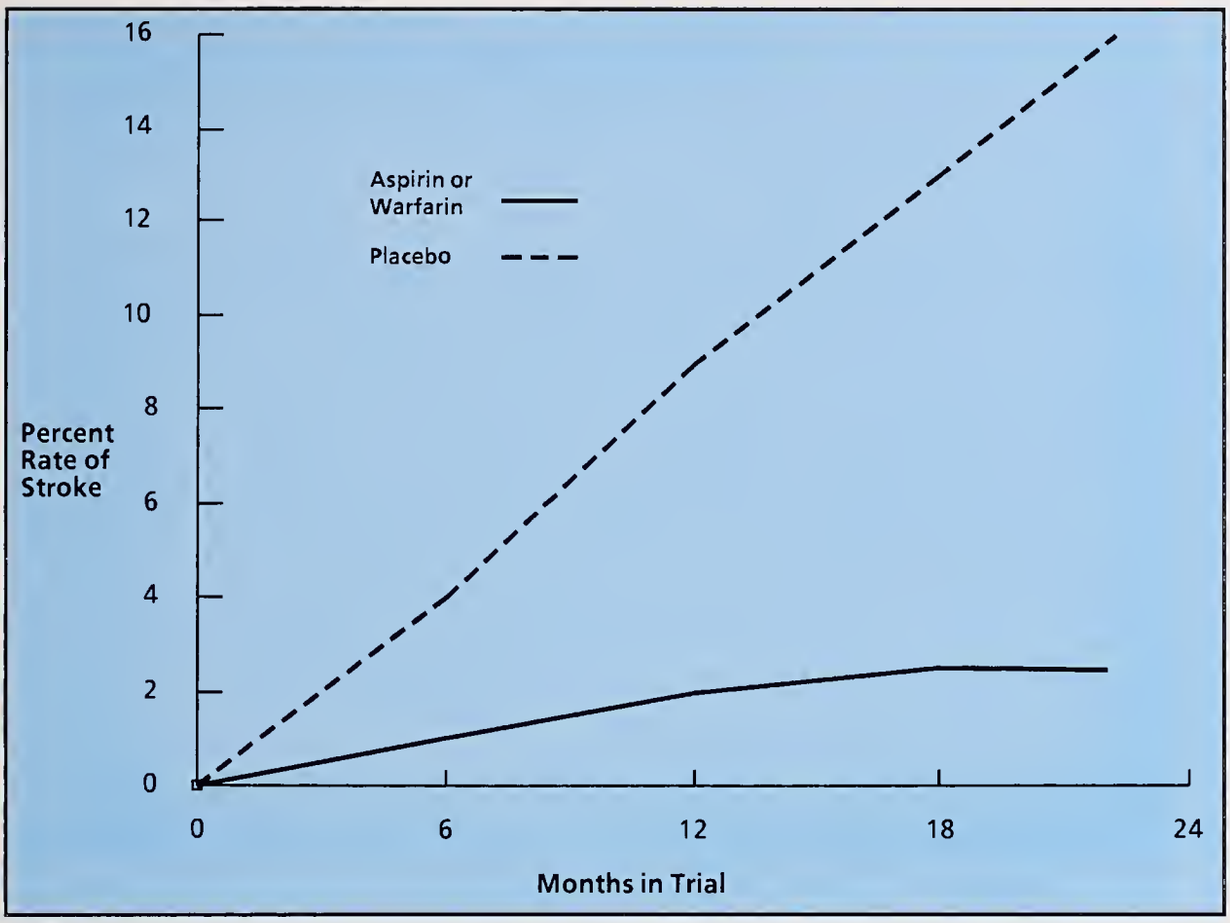
Neural Prostheses. The first electrical neural recordings from the brain using microelectrodes that contain integrated electronic amplifiers were accomplished in 1989. Brain activity recorded with such electrodes offers the promise of a reliable system for generating commands to control prosthetic muscle stimulators in paralyzed individuals. A new electrode implanted through the skin with a hypodermic needle and designed to stimulate paralyzed muscle has been investigated. The result is that 80 percent of these electrodes remain functional 1 year after implantation. A quadriplegic who received the first implanted functional neuromuscular stimulation system has had the implant for 3 years now and has had no significant complications.

Epilepsy. It is estimated that approximately 2 million people in the United States have epilepsy, of which there are several forms, each with different causes and symptoms. New methodologies are being developed to detect, prevent, and treat the different types of seizures, as well as to assess the effects of seizures and seizure therapy on learning and behavior. Although new drugs that have emerged from the NINDS Antiepileptic Drug Development Program are effective for many patients, some types of seizures are resistant to drug therapy. In selected cases surgery is now used. More research is needed to understand the forms of epilepsy and to develop more effective drugs and surgical techniques.

Stroke Research and Interventions. Indications are that stroke incidence is increasing despite the continuing decrease in mortality; also, as the mean age of the population continues to rise, the population at risk for stroke is even greater. A major gap in knowledge about stroke concerns the differences in incidence and mortality in minority groups versus nonminority populations. A new 5-year study has begun to examine the recurrence of stroke in black and Hispanic-American populations. The results of this study could provide important information that could be used to prevent the added stroke risk in these populations. Identifying risk factors through epidemiologic studies is of the utmost importance in preventing death and disability from this major health problem.

The preliminary results of an exciting new study supported by NINDS indicate that therapy with either aspirin or the anticoagulant drug, warfarin, is effective in the short term in reducing the risk of stroke in elderly patients with atrial fibrillation. Those who took aspirin or warfarin had 81-percent fewer strokes. The trial is continuing in order to address the relative benefits of aspirin and warfarin.

One of the key research issues over the next decade will be medical management of patients during the stroke episode, which can mean the difference between returning to active daily living versus



Rates of stroke in patients given active therapy versus placebo.

being left speechless or paralyzed and dependent on family and health care. Recent studies suggest that a large proportion of brain tissue is not irreversibly damaged until hours after the initial stroke. This provides an opportunity to limit brain damage from stroke.

Investigators have completed a pilot safety study of tissue plasminogen activator (TPA) to treat the acute ischemic stroke. TPA dissolves blood clots that are plugging arteries. Although brain hemorrhages are a risk of this treatment, TPA may offer improvement for selected patients if given soon enough after the stroke begins. A clinical trial will be required to substantiate this study. TPA is potentially a most useful agent for treating acute stroke, but it must be shown that when given early it will reestablish blood flow and prevent permanent brain injury at an acceptable level of risk.

Heparinoid is a new drug derived from heparin. It can prevent the formation of blood clots in blood vessels, but it has less risk of causing blood vessels to hemorrhage than the widely used heparin. In pilot studies, heparinoid was shown to be safe enough to give to stroke patients, and there was evidence that it might be an effective treatment for preventing the progression of brain injury after some strokes. A clinical trial has been organized to determine if heparinoid improves outcome in patients after stroke.

Head and Spinal Cord Injury. Every 15 seconds a traumatic injury to the head or spinal cord occurs; every 5 minutes the injury kills someone; every 7 minutes a victim who survives is doomed to a life of permanent brain or spinal cord damage. There is substantial evidence that if the patient's brain or spinal cord can be protected within 4 hours of damage,

permanent damage can be prevented in a large number of cases. Work is continuing toward understanding injury to the nervous system, and there are exciting leads for new treatment strategies.

Recent research on injury and regeneration in the nervous system has led to optimism that injured neurons can survive and that regrowth is possible. However, the most basic questions still need to be addressed. For example, it is not known when neuronal cell death is complete; how long the injured axons can sustain regeneration; whether glial cells retain their normal characteristics; and if blood supply returns to normal after injury.

Implantation of tissues, cells, and cellular products into the central nervous system continues to offer promise for the treatment of spinal cord injury. Components of the nervous system and of placental tissue appear efficacious in the growth of nerve fibers. One new area of potential treatment for central nervous system trauma is the use of nervous tissue from fetal animals to replace damaged areas of the adult brain or spinal cord. Work is needed to understand the interactions of the host nervous system and the implanted tissue, to demonstrate the long-term survival and growth of the implants, and to assess the potential of the grafts to restore lost function.

An exciting new clinical trial recently has reported that patients treated with the corticosteroid methylprednisolone within 8 hours of spinal cord injury showed significant improvement in motor function and sensation as long as 6 months after injury. Patients evaluated in the emergency room as having neurologically complete or incomplete spinal cord injuries benefited from the drug. Investigations of methylprednisolone will continue.

Neuro-AIDS Research. The devastating effects of acquired immunodeficiency syndrome (AIDS) are particularly apparent in the nervous system. Thirty percent of AIDS patients experience neurological complications early in the course of their illness; more than 70 percent suffer from neurological problems as the disease progresses. Recent findings indicate that the viral material in neuro-AIDS differs from that found in patients who do not exhibit neurological involvement. Examining the mechanism and implications of this phenomenon is a high priority. Research is in progress to determine how the virus enters the brain through the usually impenetrable "blood-brain barrier" and how it damages nerve cells. Understanding these phenomena may allow researchers to prevent or ameliorate the neurological symptoms of AIDS.

Basic Neuroscience Research. The foundation of present knowledge about disorders of the brain and nervous system is built on basic neurological research. In the past decade, basic research produced an enormous expansion of insights into the structure and function of the nervous system. New information in molecular and cellular neurobiology has provided unprecedented opportunities for scientific advancement and clinical breakthroughs. Nevertheless, understanding of the underlying mechanisms involved in many neurological disorders remains incomplete. To continue achieving clinical successes, the focus must be maintained on the basic research that leads to clinical applications, for it is only through a strong science base that the potential of the "Decade of the Brain" will be realized.

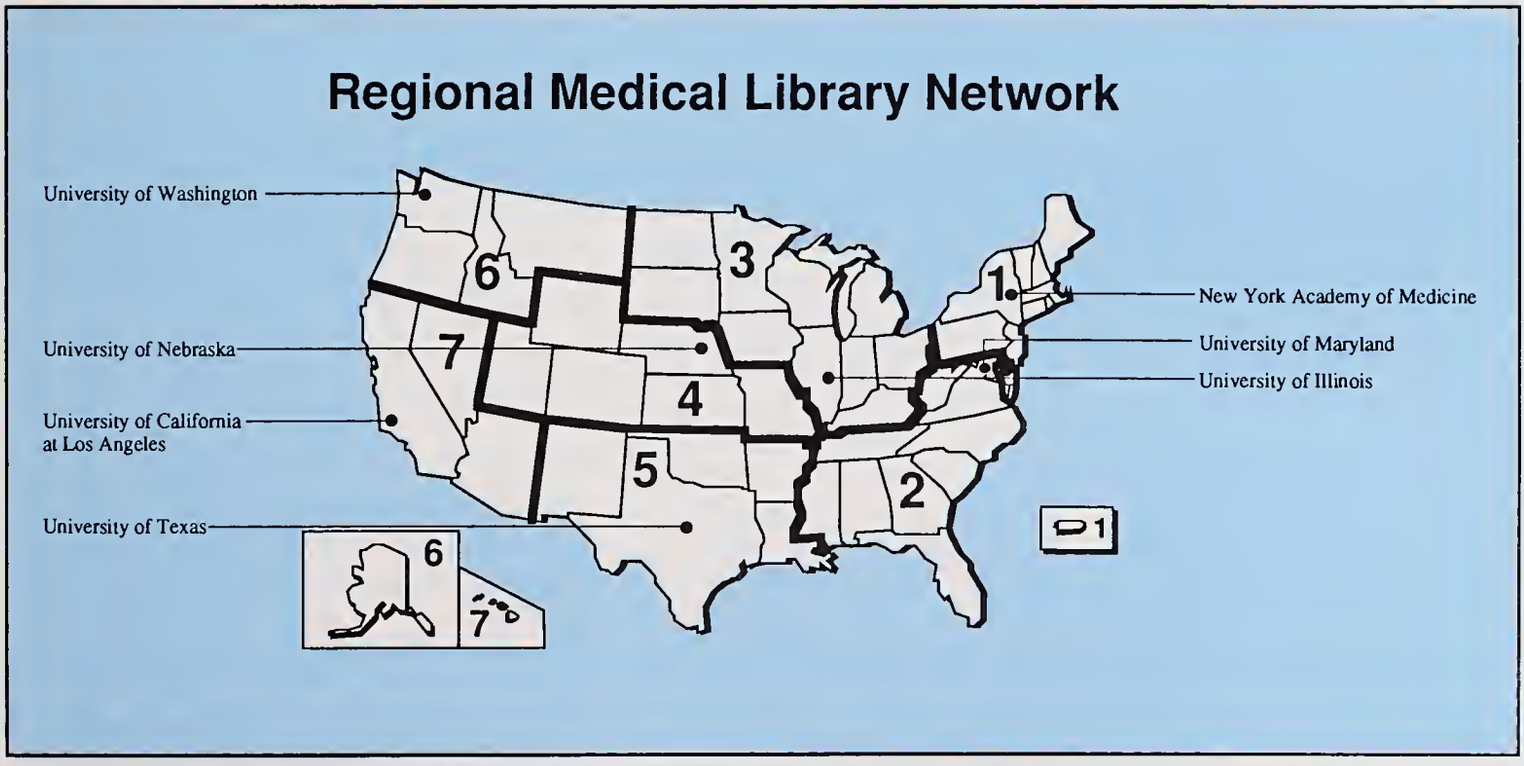
National Library of Medicine

Director's Preface

The National Library of Medicine (NLM) is responsible for meeting the information needs of our Nation's physicians, research scientists, and other health care professionals as they strive to improve our public health. The Nation spends tens of billions of dollars a year on research and treatment of acquired immunodeficiency syndrome (AIDS), cancer, heart disease, and other afflictions. Effective biomedical information services are essential to ensure that we maximize the benefits of our enormous investment. NLM's biomedical information programs serve as a multiplier, increasing the value of the knowledge resulting from biomedical research. The more rapidly and efficiently health professionals across the country can exploit the latest knowledge gained from research, the faster we will win the fight against AIDS, cancer, and other dreaded human diseases. Guided by the Board of Regents' 1987 long-range plan, NLM directs its resources to meeting this information challenge now and in the future.

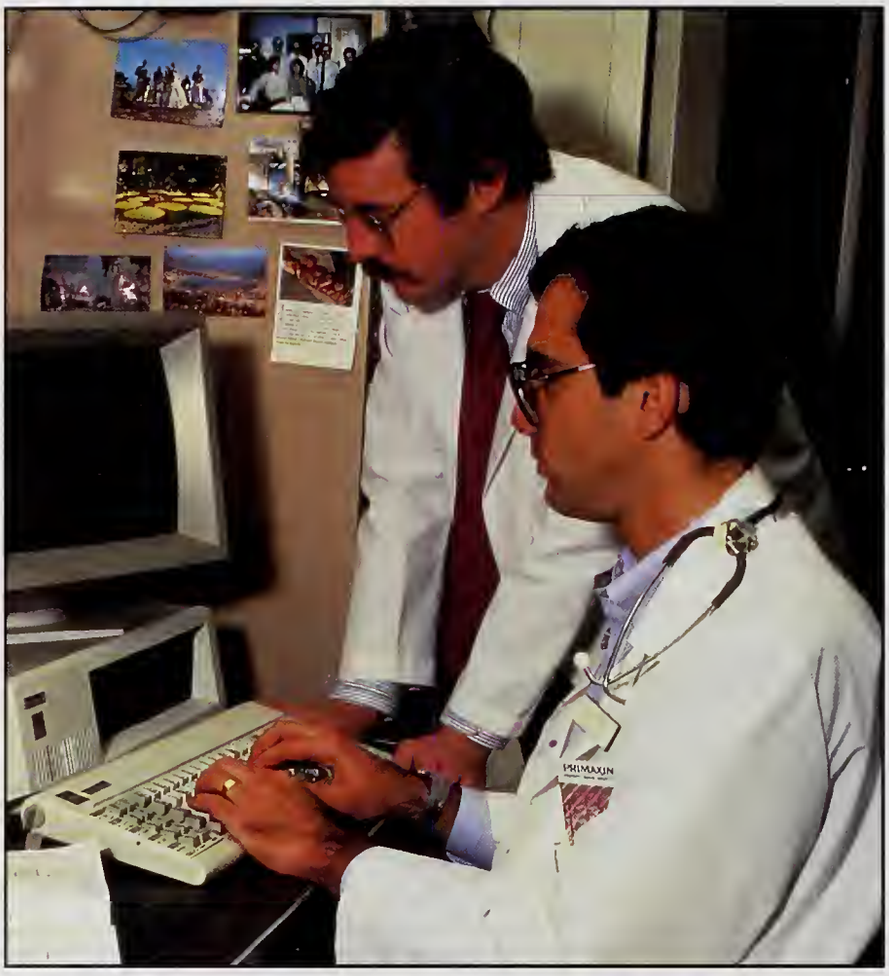
Program Highlights

Outreach Programs. At the request of Congress, through reports to the Senate appropriations committees and a 1987 amendment to the National Library of



The Regional Medical Library Network provides information services to health professionals through medical libraries serving all 50 States.

Medicine Act, NLM has initiated an outreach program. The recent report of the Board of Regents on *Improving Health Professionals' Access to Information*, published as an update to the NLM long-range plan and based on the work of a distinguished panel chaired by Dr. Michael DeBakey, recommends major enhancements to the Regional Medical Library (RML) Network; expansion of resource access grants; expansion of the Integrated Academic Information Management Systems Program; substantial increases in the number of Medical Informatics (the field dealing with medical information systems) training centers, individual awards for research, and career development and demonstration grants; and augmentation of efforts to publicize and promote the use of NLM's information products and services.



GRATEFUL MED is an easy-to-use interface to MEDLINE for health professionals.

NLM has the opportunity to increase its impact on health care, education, and research by establishing direct contact with health professionals who are the ultimate users of biomedical information services. Underlying the DeBakey panel recommendations is the belief that direct access to NLM's products and services can compensate significantly for the relatively poor status of traditional channels of health-related communication in rural and other professionally isolated communities populated by minority and other low-income groups and improve the delivery of health care in better served areas. Working in collaboration with the member libraries of the RML Network, including health science libraries at historically black schools, and with other governmental and community-based organizations, NLM will begin demonstrations to test alternative strategies for improving health professionals' access to information.

NLM is also increasing support for resource access grants and training grants. Access grants are directed primarily to small and medium-sized hospital libraries, the institutions to which health care professionals most often turn for access to biomedical publications and electronic bibliographic data bases. The DeBakey panel found that not enough persons in the biomedical fields have had training in the use of modern computer and communications systems; increased support is planned in this area.

To accomplish its outreach mission, NLM will promote the use of its current products and services and obtain more organized feedback on the use of its available information resources. GRATEFUL MED, NLM's easy-to-use microcomputer interface to the NLM system, is being widely publicized. GRATEFUL MED's use is growing rapidly; the

number of persons with copies of the GRATEFUL MED software has doubled in the past 2 years. A clearer understanding of who uses NLM's products and services and why and how particular services are chosen will aid the development of a continuous "production line"—or array—of new and enhanced products and services that are immediately responsive to user needs.

A study using the "critical incident technique" was recently conducted to explore the reasons why health professionals and researchers use MEDLINE and the impact such use has on clinical care and biomedical research. The study found that MEDLINE is a valuable resource for information on patient care, in addition to its use for research purposes and other professional activities. Participants described in detail critical incidents wherein the use of MEDLINE-derived information had an impact on their medical decisionmaking and on the lives and well-being of their patients. More than half the searches described were carried out in response to a need for information on patient care. Moreover, MEDLINE was frequently either the first choice for information or the source that came through when others failed, such as personal reprint collections, textbooks, and colleagues.

Electronic Imaging. The long-range plan encouraged NLM to consider building and disseminating medical image libraries in much the same way it acquires, indexes, and provides access to the biomedical literature. In 1989, the Planning Panel on Electronic Imaging recommended that NLM proceed with the initial phases of the Visible Human Project: the development of an image data set of the entire human body (male and female). The panel further recommended that NLM support a follow-on research effort to develop methods, tools, and standards for classifying anatomic image data from the project, so that applications may be developed that can extract, manipulate, and display image subsets on the basis of organs, tissues, body systems, and biologic function. The next phase would be to expand on initial image libraries composed of normal structure to encompass specialized image collections of related structural function, such as embryological development, normal and abnormal variations, and disease-related images. NLM should also encourage and support investigator-initiated research in imaging techniques and develop and enhance its wide-area computer network connections to provide an efficient electronic distribution mechanism for large digital files such as those encoding biomedical images. These recommendations have been incorporated into the long-range plan.

Biotechnology. The long-range plan recognized that the rapid increase in information about molecular biology was outpacing the current systems for acquiring, storing, and disseminating these data in electronic format and recommended that NLM initiate a national program to deal with this problem; Congress established the National Center for Biotechnology Information (NCBI) in November 1988. The goal of the center is to develop new ways to link together the existing data bases as well as create new ones, and to provide integrated computer systems that will furnish easy-to-use access to the data bases and to analytic software. To this end, and building on NLM's long experience with managing biomedical data bases, NLM informatics specialists are identifying and indexing new DNA and protein sequences, creating new sequence records from the 3,500 journals that are regularly scanned for the MEDLINE data base. The goal of this data base, called the GenInfo Backbone, is to provide a core of biological information about sequences, including the sequence itself, that will be available to researchers within a month of publication. In

conjunction with the building of the GenInfo data base, standard gene name nomenclature is being collected from appropriate sources, including scientific societies and stock centers. In addition to data base building, NCBI provides funding in conjunction with other NIH institutes and the National Science Foundation to enhance the connectivity of existing data bases.

A multidisciplinary research group of computer scientists, molecular biologists, biochemists, and structural biologists has been recruited to investigate fundamental problems in gene organization and protein structure and to develop new models and algorithms for sequence analysis. Another major activity is to develop new software tools and systems for information retrieval and analysis. The program also provides grant support in computational molecular biology. The scope of such support is quite broad and includes research into methods and algorithms for improving the efficiency of information retrieval and improving the efficiency of analytical operations that are computationally intensive.

Unified Medical Language System (UMLS). The long-range plan strongly endorsed continuing the development of the UMLS, which will make the myriad classifications of medical knowledge invisible to the user and retrieve and integrate related machine-readable information from multiple sources, without imposing a single vocabulary on all systems and users. The DeBakey panel recognized the importance of the UMLS in implementing new products and services for the biomedical community: the development of "bridging" linguistic structures that link like concepts in disparate classification systems will facilitate advances in all areas of medical information processing and therefore have a significant effect on biomedical research and health care practice.

NLM and its contractors have been able to report significant progress on UMLS, including the development of Meta-1, the first version of the UMLS metathesaurus, or central vocabulary source; establishment of the basic categories or semantic types to be included in the first version of the UMLS semantic network; definition of the initial version of the UMLS information sources map, which will describe available machine-readable sources of biomedical information; and interim improvements to existing information services and prototypes of UMLS features and components.

AIDS Information Services. The Health Omnibus Program Extension of 1988 (Public Law 100-607) calls for NLM's involvement in the establishment of a "data bank on information on the results of research with respect to acquired immune deficiency syndrome conducted in the United States and other countries" (Section 2317 (C)). Current information services include AIDSLINE, containing more than 23,000 references to scientific articles about AIDS selected from MEDLINE, CANCERLIT, and the Health Planning and Administration data base; DIRLINE, (NLM's on-line directory of organizations that provide information) enhanced with an AIDS component in collaboration with the Centers for Disease Control's National AIDS Information Clearinghouse; AIDSTRIALS, describing ongoing clinical trials; AIDSDRUGS, describing each agent being tested in these clinical trials; and the printed AIDS Bibliography, containing citations to AIDS literature referenced in MEDLINE and in NLM's collection of books and audiovisuals.

These steps are only the beginning of the development of a comprehensive AIDS information service. To ensure timely dissemination of scientific and medical information to the biomedical community, a comprehensive AIDS information service is needed to provide faster access to more complete U.S. and international

information. Plans are under way by NLM to improve the currency of information in AIDSLINE; incorporate into AIDSLINE references to a broader range of publications; enhance existing information retrieval systems and investigate gateway access methods to connect to relevant AIDS information resources available elsewhere; and initiate a series of special AIDS bibliographies focused on particular topics and audiences.

Summary

The increase in knowledge and advances in health care resulting from our Nation's investment in biomedical research would be of limited value if it were not for NLM's function of organizing and providing access to biomedical information. The end products of these activities are enhanced medical research, education, and practice, and improvements in the public's health and quality of life.

National Center for Human Genome Research

Director's Preface

The Human Genome Project (HGP) is a scientific research effort to study the genetic underpinnings of humans and other living things. Its goal is to provide biomedical researchers with maps of human chromosomes and detailed information about the order of the chemical subunits of human DNA. Biomedical researchers will use these tools well into the next century to understand human physiology and disease. With chromosome maps, DNA sequence information, and new machines, scientists will be better able to understand and eventually treat the more than 3,000 genetic diseases that afflict human beings. These technologies will also be applied to understanding the mechanisms of common diseases in which genetic predisposition plays an important role, such as heart disease, cancer, and Alzheimer's disease.

In the United States, the HGP is supported by the National Center for Human Genome Research (NCHGR) and the Department of Energy's (DOE's) Office of Health and Environmental Research. The agencies have been collaborating on the project under the terms of a memorandum of understanding signed in October 1988. NCHGR and DOE have developed a joint 5-year plan that sets three explicit goals to achieve the mission of the project:

- to construct maps of human chromosomes and determine the order of the chemical subunits (nucleotides) of human DNA;
- to create computer data bases, repositories for research materials, and other common resources to enable wide access; and
- to develop new technologies necessary to achieve the first two goals. Such technologies will in most cases be applicable to a wide range of research and commercial uses.

Scientific Objectives of the Human Genome Project

NCHGR research focuses on advancing the capabilities of new technologies for analyzing DNA, to increase the speed and reduce the cost of these technologies and thereby enable scientists to address genetic research problems more quickly and efficiently.

Nearly 100,000 genes are contained on the 23 pairs of chromosomes in human cells. Each chromosome consists of DNA and proteins associated with it. The DNA consists of extremely long strands of nucleotide bases intertwined in a double helix. There are four nucleotides bases in the DNA of all living organisms—abbreviated A, C, G, and T. The genetic information of a cell is contained in the order of the nucleotides.

A gene is a stretch of DNA that codes for a product, usually a specific protein. We know about most human genes because of mutations that cause them to malfunction. A change in DNA—a missing fragment or replacement of one base by another—causes the production of a protein that does not work normally. Such an aberration can cause a disease.

The recent discovery of a malfunctioning gene that causes cystic fibrosis (CF) illustrates the success of gene mapping and sequencing strategies in finding disease-causing genes. Those scientists, however, did not have the research tools the HGP plans to provide: access to genetic linkage maps, physical DNA maps, and DNA sequence data of the entire human genome. Because investigators looking for the CF gene had to begin their search from scratch, their exploration was long and arduous. The search for the CF gene is, however, a small-scale example of the steps that will be required to map and sequence the entire human genome.

So far, most genetic diseases are defined by how they are inherited in families. The first step in finding a disease gene is to correlate inheritance of the disease with the inheritance of markers on a genetic linkage map of the human chromosomes. The map consists of a set of markers used to trace the inheritance of chromosomal segments back to each parent. After studying many families and determining which chromosome regions are inherited with the disease, it becomes possible to link the disease gene to its approximate location on the chromosome.

Once a gene is mapped to a chromosomal region, the next step is to reconstruct a physical map of the chromosomal DNA from that region. To analyze the DNA, it is first cut into small fragments and copied or "cloned" in bacteria or yeast cells. The small fragments of cloned DNA are then reassembled in the order they appear on the original chromosomes.

Once the DNA is copied and ordered, investigators must identify which pieces of DNA correspond to the gene. Doing so requires a variety of techniques, but necessarily involves DNA sequencing. To identify the molecular defect in CF, for example, it became necessary to derive a "normal" DNA sequence for reference and compare it to DNA taken from people with CF.

Research Accomplishments

DNA Cloning

There have been many significant scientific advances in genome technology during the past 2 years. The length of human DNA that can be isolated and copied for study has increased severalfold. In 1987, investigators developed a method of constructing in yeast cells an artificial chromosome called YAC, which allowed them to copy DNA ranging from 50,000 to 1 million base pairs in length. Before that, the maximum length of cloned DNA had been 40,000 to 45,000 base pairs. YAC's have been used by several research groups to clone large segments of human DNA, and the process of putting those cloned fragments into a large-scale physical map for several chromosomes has begun.

As of December 1989, regions of 1.5 to 2 million base pairs on chromosomes X and 17 were spanned by ordered clones, creating valuable resources for the study of genes. These regions contain the genes causing hemophilia A and B in boys. This new ability to clone much larger fragments of DNA presented by YAC's greatly simplifies the process of developing physical maps of chromosomal regions and is a major step toward achieving the 5-year goal for physical mapping.

Chromosome Mapping

At an August 1989 joint NIH-DOE planning conference, consensus formed around the idea of reporting map information according to "sequence-tagged sites" (STS's). These are DNA sequences found only once in the genome, which could be used to order fragments. With STS's, laboratories of all sizes, using a variety of different mapping methods, could report their results in a common language. The STS's would serve as universal markers for genetic linkage and physical maps. This common language, if fully implemented, would enormously simplify the cross-checking of maps made by different groups.

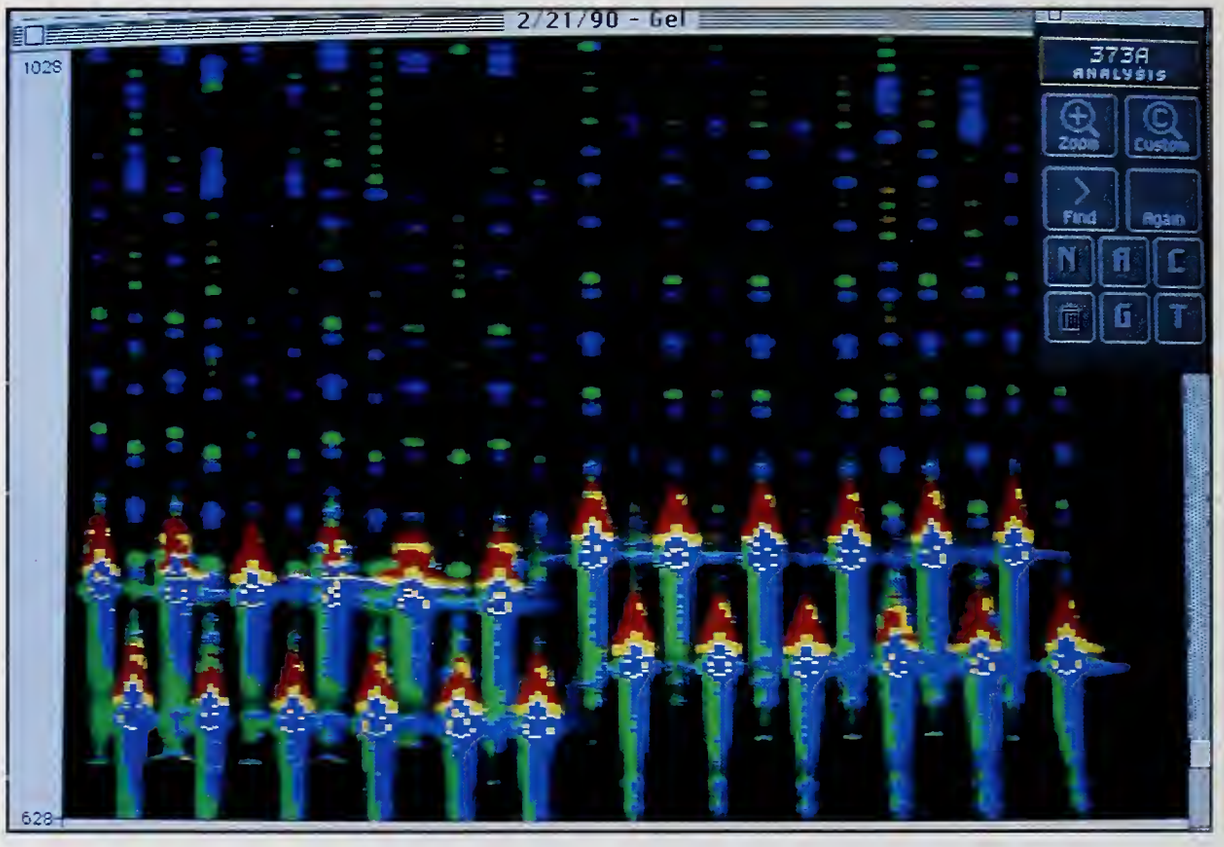
DNA Sequencing

The methods for determining the base-pair sequence of DNA have also improved markedly. NIH and DOE have funded DNA sequencing projects for more than a decade, but the scale of these projects is expanding dramatically. A meeting in October 1989 brought together scientists engaged in sequencing projects around the world. This meeting produced a consensus that the time was right to begin pilot projects to test the feasibility of large-scale sequencing.

Projects to sequence an entire bacterial genome are now under way, and even larger projects are commencing. One project has set out to sequence the entire genome of *Caenorhabditis elegans*, an intensively studied nematode worm. This worm is the largest organism in which the developmental lineage of all the cells of the body have been identified and for which there is a complete "wiring diagram" of the nervous system. Extensive DNA sequence information will provide another powerful tool for understanding these processes in even greater detail, with implications for many other organisms including humans.

Computer Data Base Management

An area of special progress, known as informatics, is the management of data bases containing the various kinds of information needed for genome research. A joint NIH-DOE task force on informatics has issued its first report and is laying out a strategy for anticipating future data storage and analysis needs so that NCHGR, DOE, the National Library of Medicine, and other organizations can better manage the coming deluge of new information on genetics research.



Determining the sequence of the 3 billion base pairs in human DNA will require development of efficient, low-cost machines. This automated DNA sequencer (Applied Biosystems, Inc.) identifies nucleotides labeled with fluorescent dyes. The sequencing gel depicted on this screen contains over 12,000 bases of DNA.

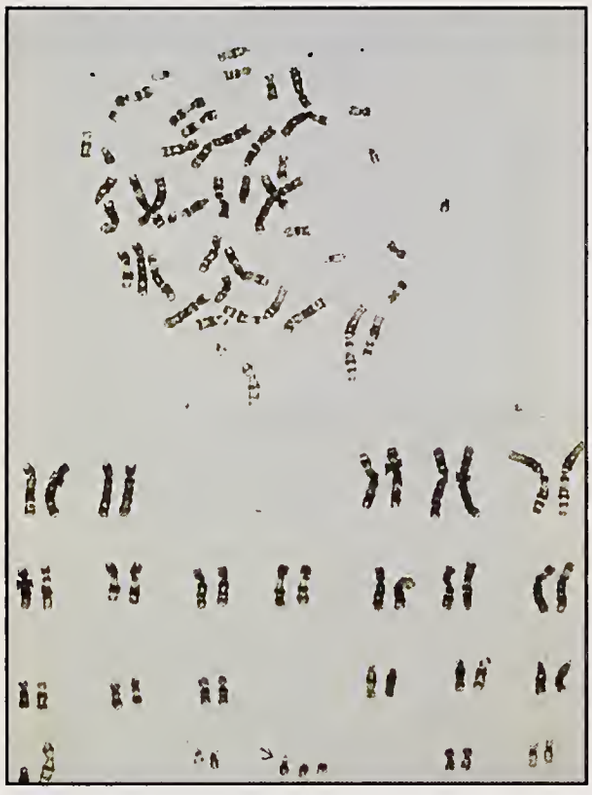
Ethical, Legal, and Social Implications of Human Genome Research

As genes are discovered and mapped, and the genetic factors that contribute to disease become better understood, difficult questions will arise about how to manage such genetic information. The same technologies used to map genes, for example, can be used as tests to diagnose genetic disorders and may serve as the basis for new treatments.

Information obtained from these tests can also harm the patient, however, unless policies to protect the interests of individuals are in place. Some have recently raised the prospect that genetic tests might be used as tools of discrimination, for example, to prevent access to employment or insurance. There is a need to devise public policies that preserve individual privacy and autonomy and yet accommodate inherent genetic variability among individuals.

NCHGR and DOE are mounting research programs focused on the social and ethical implications of genome research. By devoting approximately 3 percent of its annual budget to studies in this area, the NCHGR Bioethics Research Program constitutes the largest single funding source in the Federal Government for bioethics research.

A joint NIH-DOE Working Group on the Ethical, Social, and Legal Issues (ESLI) related to mapping and sequencing the human genome will help guide the bioethics programs. The working group will schedule workshops and public meetings to reach out to various communities likely to be affected by the new genetic technologies. The working group will serve as a two-way conduit to anticipate social impacts of genome research and communicate concerns to the scientific community, and to educate the general public about genome research. The ESLI working group also intends to formulate and debate policy options that bear on research or use of research results flowing out of the genome project.



The 24 different human chromosomes accommodate nearly 100,000 genes—hereditary units containing all the information needed to make a human being.

International Coordination

There are many opportunities for international collaboration to enhance the progress of the human genome project. Many countries are interested in participating in the project and all are interested in the outcome. Programs with funding are currently under way in the United Kingdom, Italy, and the Soviet Union. Funding is expected in the near future from the Commission of the European Community, France, and Japan.

An association of interested scientists from around the world has been formed and incorporated as the Human Genome Organization (HUGO). NCHGR plans to work closely with HUGO to support international meetings, workshops, and activities essential to efficient international data exchange.

National Center for Nursing Research

Director's Preface

The National Center for Nursing Research (NCNR) has made substantial progress in the development of its programs and goals during 1989 and 1990. Three extramural programs—Health Promotion and Disease Prevention; Acute and Chronic Illness; and Nursing Systems—and a new intramural program form the basis for NCNR research activities. Through these programs, nursing research explores approaches to maintaining health, examines how physical and social environments affect health and illness, evaluates nursing practices and interventions as they relate to patient outcomes, and addresses issues affecting the care of individuals and families in a variety of settings.

National Nursing Research Agenda

NCNR is working with the National Advisory Council for Nursing Research and priority expert panels to assess and refine nursing research objectives in seven areas: low birth weight; the care of patients infected with human immunodeficiency virus (HIV); long-term care for older adults; symptom management; nursing information systems; health promotion for children and adolescents; and technology dependency across the lifespan.

Centers of Excellence in Nursing Research

As part of a new centers program established in fiscal year 1989, the Center for Women's Health Research and the Center for Advancing Care in Serious Illness were funded as specialized centers; the Center for Research in Critical Care Nursing and the Center for Nursing Research in Long-Term Care of the Elderly were funded as exploratory centers. Specialized centers support interdisciplinary research by established investigators in specific basic or clinical research areas and provide an environment for research training and career development. Exploratory centers enable institutions with some ongoing research to strengthen their capabilities and generate new research through interdisciplinary efforts.

Research Training Initiatives

NCNR continues to increase the number of its nursing research trainees, especially postdoctoral trainees. Incentives to increase the number of minority trainees have also been announced. All competing applications for Institutional National Research Service Awards must include plans to recruit and train minority nurses. Institutions with current training grants are encouraged to request administrative supplements to add minority trainees. Specialized center grants require plans to recruit and train minority nurses in research and establish links with minority nursing faculty. In addition, NCNR urges principal investigators with at least 2 years of support remaining on their grants to request administrative supplements for minority undergraduate students, graduate research assistants, and minority faculty. Two minority supplements were made to institutional research training grants and one to a research project grant.

In addition, in response to a recommendation by the 1989 NCNR-sponsored workshop on bioethical issues, NCNR issued a program announcement to stimulate research training and career development in bioethics and clinical decisionmaking. NCNR also announced interest in research training applications to study family caregiving in Alzheimer's disease (AD) and other dementias.

Scientific Advancement and Opportunities in Nursing Research

Human Immunodeficiency Virus. The combined biological and psychosocial perspectives of nursing science can contribute significantly to reducing the risk of HIV exposure and improving nursing care interventions. The physical, psychological, and social problems associated with HIV infection require complex decisions about the delivery and evaluation of nursing care. An NCNR-supported researcher is assessing care needs of HIV patients in different treatment settings. Another study is documenting patient care needs in response to physical symptoms of HIV, life stressors, and mental status at various stages of the disease.

The quality of the nursing care provided to *Pneumocystis carinii* pneumonia patients with HIV is being measured during a 6-month period beginning with their first hospitalization. Patients and nurses have been interviewed about the most common problems of these patients. Responses have included loss of physical health, mental capability, mobility, and control of urine and bowel function. Nursing interventions to ameliorate these problems will be evaluated.

Better methods to detect HIV-infected infants are needed to offer earlier and potentially more effective care. Newborns may test positive for HIV because they are carrying the mother's antibodies temporarily. An NCNR grantee is comparing high-risk infants who remain HIV positive during the first 15 months of life with infants who test negative or convert to negative. Factors that may affect a child's risk of infection, such as prenatal care and maternal HIV antibody status, are being examined, as well as infant growth and development.

NCNR is initiating a Collaborative Intramural Program for HIV infection research, with the National Institute of Allergy and Infectious Diseases (NIAID). NCNR investigators will conduct basic and clinical research, working with the NIAID intramural program and the NIH Clinical Center. The goals are to reduce patient dysfunction and suffering from the physical or psychosocial sequelae of HIV infection, such as unintentional weight loss, decreased appetite, diarrhea, fatigue, oral complications, depression, and dementia.

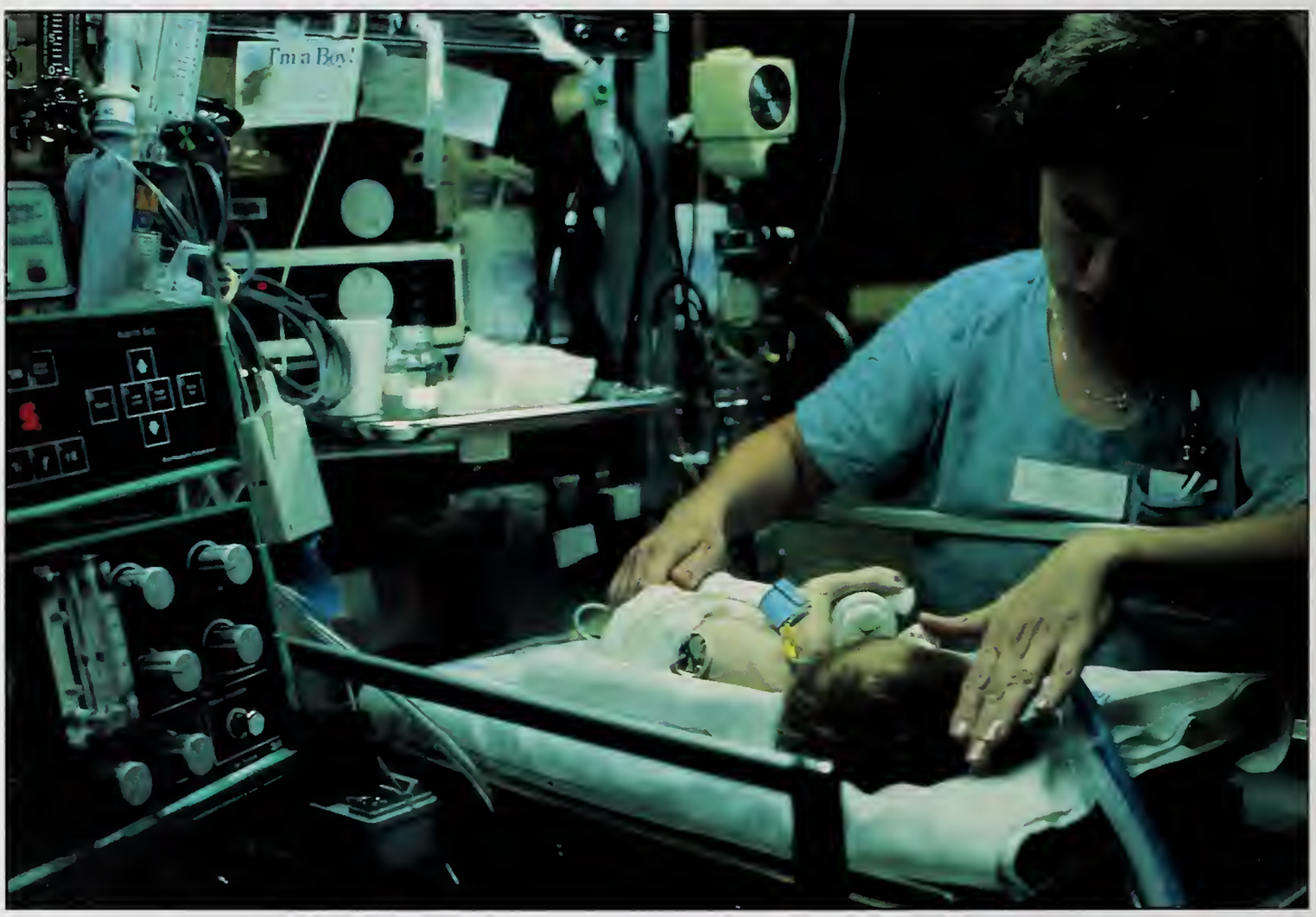
Caregiving for Older Adults. Because of reduced hospital stays and an aging population, research is needed on the types, quality, and settings of care, and the effects on family caregivers, especially older caregivers. In collaboration with other funding agencies, NCNR has invited applications on caregiving for patients with AD and other dementias.

NCNR studies under way include testing mental stimulation techniques for caregivers of AD patients to use at home, and examining memory and behavior problems to develop programs and methods for assisting home caregivers in dealing with the demands of AD patients. Grantees are testing selected nursing interventions for stress in older family caregivers and cultural factors that affect caregiver perception and burden. Also being examined are the patterns of rural home care and community support for older adults, including those with AD and hip fracture. In addition, NCNR and the National Institute on Aging are collaborating on clinical trials to reduce frailty and injuries in older people.

Low Birth Weight and Infants at Risk. Nursing research on low birth weight addresses four major areas: maternal health before conception, prenatal care, hospital care of the infant, and care of infant and family after discharge. An NCNR grantee has developed a feeding routine using a self-regulating, slow-feed nipple (similar to breast feeding) in combination with gavage (tube) feeding for preterm infants. Infants on this routine had a weight gain almost three times that of infants in the standard feeding routine, cried less, and slept more soundly.

An NCNR study is evaluating the effects of prenatal and postpartum nurse home visitation on enhancing the health and well-being of poor, unwed women and their first-born children. Another research project is developing and testing social support interventions for pregnant, low-income, black women. Other studies include the effect of maternal stress on the sleep behavior of vulnerable infants to identify children at risk for health and developmental problems; the effects of pregnancy, stress, and social support on the family; and homelessness and pregnancy.

NCNR has issued a program announcement in collaboration with the National Institute of Child Health and Human Development to study physical care for low birth weight infants, particularly interdisciplinary studies on infant feeding, respiratory support, physical positioning, and skin care.



A nurse observes a low birth weight infant in a study to improve endotracheal suctioning (removing fluids that collect in the airway).

Diagnosis and Treatment of Pressure Sores. Pressure sores cause human suffering, financial burden, and delayed rehabilitation. One NCNR investigator is testing a method for predicting the risk of pressure sores in home, hospital, and nursing home patients. Another project is determining the effectiveness of transcutaneous electrical nerve stimulation, which enhances the blood supply to tissues and appears to speed wound healing. Findings are expected to contribute to the development of procedures to increase healing rate, reduce the length of hospitalization, and limit debilitation.

Nursing Resources and Patient Care Delivery. Research is critically needed on effective long-term alternatives to the nursing shortage. An NCNR researcher has examined factors found to increase staff nurse satisfaction and retention, such as control over practice and resources, participation in decisionmaking, interdisciplinary planning, continuity of care and home visits, and flexible work hours. Another study is comparing contract nursing units and noncontract units in terms of job satisfaction, patient satisfaction, and quality and cost of care in a large university hospital. An NCNR grantee is examining nursing management and nurse retention to facilitate better understanding of staff relationships, productivity, and quality of care. Investigators are also studying nurse retention in neonatal intensive care units and comparing patient outcomes, cost, and staff satisfaction in specialized and nonspecialized units caring for AD patients.

Minority Health. In addition to research on minority maternal and child health, NCNR supports other projects to improve the health of minority populations. One NCNR grantee is developing a program in black churches to teach hypertensive congregants about managing medications, diet, exercise, and stress to control their hypertension. Another project is assessing changes in physical and mental health, socioeconomic resources, and use of health and community services by Hispanic-American older people. Researchers are also developing a better understanding of the cultural concepts of health, aging, and medical treatment to help health care workers provide more effective care.

Researcher measures the blood pressure of a woman participating in a study on health and aging among Hispanic-American older people.

Bioethics and Clinical Decisionmaking. Modern technology poses many complex bioethical dilemmas for patients, families, and health care workers. Often, these dilemmas involve decisions about informed consent, refusal of treatment, life-sustaining technology, terminal illness, and vulnerable populations as subjects in research. An NCNR-sponsored workshop on bioethics and clinical practice assessed available research and examined promising approaches to future research. NCNR will support feasibility and pilot studies on this subject, emphasizing an interdisciplinary perspective.

Rural Health. National concern about the quality and efficacy of rural health care, facilities, clinical services, and delivery systems is growing. All NCNR priority areas have a rural health component, especially low birth weight and long-term care. NCNR is collaborating with other Public Health Service (PHS)

organizations to develop and test community-based models to increase access to health care in rural areas. Currently, NCNR is funding two projects testing innovative practice models in rural hospitals. Other studies include approaches to reduce risks for cardiovascular disease in rural school children, factors that affect healthy functioning in rural patients with multiple sclerosis, and home care for older adults in a rural area.

Effectiveness of Patient Care. Congress expressed interest in NCNR participation in the PHS initiative on the quality and effectiveness of health care and the inclusion of nonphysician health care providers. The Agency for Health Care Policy and Research (AHCPR) is administering this initiative, and NCNR and AHCPR are collaborating in the area of patient outcomes research.

Women's Health. NCNR supports research topics addressed in the 1985 PHS Task Force on Women's Health Issues, including research on conditions unique to women, how behavioral and social factors interact with biological factors to affect women's health, and how cultural conditions and socialization practices affect the health of women differently from men.

Factors related to premenstrual syndrome (PMS) are not well understood, yet PMS causes severe symptoms in many women. An NCNR project is investigating patterns and relationships of ovarian hormones, autonomic nervous system arousal indicators, and personal and social environmental factors. Investigators are also studying gut functions in menstruating women. Other women's health studies include problems of recovery in older women after myocardial infarction, and an assessment of the role of physical activity on bone mineral density in midlife women. In addition, researchers are testing noninvasive methods to manage urinary incontinence.

Directions in Nursing Research

From 1986 to 1990, the areas of research focus for nursing have taken shape. Priority expert panels are identifying crucial health questions that nursing science can and should address. NCNR will continue to collaborate with the Division of Nursing to improve the environment in which nurses practice, and with AHCPR on the effects of nursing practice on patient outcomes. Training the scientists needed to conduct nursing research, particularly increasing the pool of postdoctoral and minority applicants, will remain a top priority of NCNR. The intramural and centers programs will provide fertile environments for interdisciplinary research; and NCNR will encourage increased interface between the biological and behavioral sciences as they relate to nursing practice. Bioethics and clinical decisionmaking have the potential of becoming the focus for important interdisciplinary study. Minority health and the health of rural populations will also receive special attention.

John E. Fogarty International Center for Advanced Study in the Health Sciences

Director's Preface

The John E. Fogarty International Center (FIC) for Advanced Study in the Health Sciences is the international arm of NIH. For more than 20 years, FIC has sought to facilitate worldwide scientific cooperation, and its success has made NIH a leader in international biomedical research.

International cooperation is a critical factor in the prevention and treatment of diseases for both scientific and economic reasons. Major advances are frequently made when diseases are studied in populations living under conditions unlike those in the United States. This is particularly the case for cancer, parasitic diseases, and now acquired immunodeficiency syndrome (AIDS). Increasingly sophisticated scientific techniques strain national science budgets, in turn leading to greater cooperation in such fields as neurobiology and genetics research.

Throughout its history, FIC has fostered international cooperation through various key undertakings: funding basic research and training programs, administering bilateral and multilateral agreements, and supporting conferences and special studies. In fiscal years (FY's) 1989 and 1990, FIC began a multiphase planning effort that involved the participation of the FIC Advisory Board and prominent experts in biomedical research and health policy. Four overarching goals that stress opportunity and innovation were defined for FIC: identify and implement advanced study opportunities on the emerging scientific challenges of the 1990's; devise research and training programs for U.S. and foreign scientists that capitalize on new opportunities for cooperation in international research; identify and promote innovative opportunities for bilateral, multilateral, and regional cooperation; and strengthen FIC support for the international research efforts of other NIH components.

Research Accomplishments

FIC supports biomedical research fellowships for U.S. and foreign scientists, giving junior, midcareer, and senior scientists the chance to work collaboratively in the laboratory. Fellows conduct research on a variety of biomedical areas including infectious diseases such as AIDS and dengue fever; chronic illness such as cardiovascular and neurological diseases, cancer, arthritis, and diabetes; and other conditions such as aging, human development, and communicative disorders.

Programs for U.S. Scientists. FIC supports research fellowships for U.S. scientists—the Senior International Fellowship (SIF) Program provides support for senior U.S. scientists to conduct biomedical, behavioral, and health research in foreign research centers. In FY's 1989 and 1990, FIC funded about 80 SIF awards. Working with colleagues in foreign countries, these SIF's have made important findings on the brain's molecular self-repair process after injury and on the role of complex carbohydrates in the pathobiology of human immunodeficiency virus (HIV).

FIC also administers fellowships funded by organizations in Finland, the Federal Republic of Germany, France, Ireland, Israel, Japan, Norway, Sweden, Switzerland, and Taiwan. During FY's 1989 and 1990, more than 20 U.S. scientists received these fellowships and conducted advanced research on cancer, immunology, epidemiology, arthritis, AIDS, and molecular biology.

Programs for Foreign Scientists. FIC brings foreign scientists to U.S. laboratories for cooperative research and training through the International Research Fellowship (IRF) Program, the Scholars-in-Residence Program, the NIH Visiting Program, and the FIC's International Training Grants in Epidemiology Related to AIDS Program.

The IRF supported research training for 200 junior foreign investigators from 40 countries in American laboratories in FY's 1989 and 1990. Among their achievements was the development of a simple, reliable diagnostic blood test for the viral disease dengue fever. In an IRF followup study, the research fellows were found to be prolific researchers and to have made significant contributions to the world's scientific literature.

Fogarty scholars-in-residence are internationally renowned foreign and U.S. scientists. In FY's 1989 and 1990, more than 20 scholars pursued studies at NIH on such topics as T-cell immunity vaccines, calcium's role in muscle function and cardiac failure, and genetic markers for coronary disease susceptibility. Present and past scholars published 120 scientific papers during the past 2 fiscal years.

FIC administers the NIH Visiting Program, which invited about 3,300 talented foreign scientists to NIH to work or train with senior intramural investigators during FY's 1989 and 1990. Approximately one-third of NIH's intramural laboratory scientific staff are foreign scientists in the Visiting Program.

Fogarty scholars-in-residence discuss a challenging research topic. The FIC Scholars-in-Residence Program brings eminent U.S. and foreign scientists to NIH to conduct advanced international studies in collaboration with NIH scientists.

FIC significantly expanded its AIDS training and research programs, which are designed to increase the numbers of epidemiologists and other scientists working on AIDS worldwide, especially in developing countries. FIC international training grants in epidemiology related to AIDS were awarded to 10 U.S. institutions. About 225 investigators from more than 20 developing countries participated in this training program and conducted such studies as an epidemiologic survey of Haitian immigrants living in Miami and the use of oral mucosa to assess the status of AIDS patients' immune systems.

The program also provided 25 short-term courses in laboratory and research techniques for 1,000 junior health care personnel, technicians, and nurses.

Programs for U.S. and Foreign Scientists. FIC's International Postdoctoral Research and Training Grants in AIDS Program supports cooperation between American and foreign scientists. In the past 2 fiscal years, FIC supported 4 U.S. institutions, which provided advanced research training for 30 foreign and 6 U.S. investigators. Studies included defining the clinical and laboratory features of the AIDS-related Kaposi's sarcoma and developing a transgenic mouse model of HIV-1.

FIC also supports short-term exchanges of American and foreign scientists involving 10 foreign countries: 45 U.S. and 80 foreign scientists participated in FY's 1989 and 1990. Studies included the effects of radiation on humans and hormonal regulation of brain development.

Bilateral Agreements. FIC also fosters international cooperation by administering NIH involvement in more than 70 bilateral agreements with foreign nations or multilateral organizations. In FY's 1989 and 1990, the FIC, representing NIH, added AIDS and primatology to the U.S.-U.S.S.R. Health Agreement; created and managed a fund for implementing NIH projects under the U.S.-Brazil Presidential Initiative in Science and Technology; negotiated the memorandum of understanding between NIH and the Bulgarian Medical Academy; completed an agreement with Thailand's Chulabhorn Research Institute for a cooperative research and training program; negotiated a new science and technology agreement with Hungary that will

The cover of the *Harvard AIDS Institute Monthly Report* showcases one of FIC's AIDS programs. The training of these researchers from many nations is funded by FIC grants.

provide joint support for environmental, medical, and other studies; and forged a new cooperative health agreement with Egypt.

Activities With AIDS Organizations. FIC provided technical help to the World AIDS Foundation (WAF) and the French and American AIDS Foundation by providing scientific and administrative support to the Scientific Advisory Committee of WAF. Research grants funded by WAF involved such efforts as short-term training for clinicians and allied health professionals and technicians, and the development and testing of new approaches to prevent the spread of HIV. The FIC International Network for AIDS Research and Training held three meetings in 1989 and 1990 to facilitate communication among U.S. researchers and representatives of the World Health Organization (WHO) and others involved in international AIDS research. FIC also represented NIH at WHO committee meetings on AIDS vaccine development.

Studies and Scientific Meetings. FIC conducts studies and organizes strategy sessions on critical scientific issues. During FY's 1989 and 1990, FIC organized and cosponsored an international workshop (with the National Cancer Institute and the Cancer Institute of the Chinese Academy of Medical Sciences) on the cause and prevention of liver cancer, which defined strategies for preventing the disease in high-risk persons; a workshop (with the National Institute of Dental Research and WHO), which recommended priorities for future international collaboration in oral health research; and a conference (with the National Institute of Allergy and Infectious Diseases, and Rockefeller University) on the evolution of viruses and viral diseases.

Future Opportunities

Strengthening Health Research Cooperation With Latin America and the Caribbean. During the past 2 fiscal years, FIC has launched a Latin American Initiative to multiply scientific ties with Latin America and the Caribbean. The need for such increased cooperation was detailed in two technical papers jointly published in FY 1989 by FIC and the Pan American Health Organization: "Education and Training Needs for Medical Entomology in the Americas" and "Strengthening Health Research in the Americas Through International Collaboration."

In FY 1990, FIC began three major activities: an aggressive campaign to publicize NIH research opportunities throughout Latin America; the building of a communications network among U.S. and Latin American investigators and institutions; and the development of opportunities for U.S. and Latin American researchers to work in one another's laboratories to develop cooperative research projects. When fully funded, FIC will support international supplements to domestic grants, expansion of IRF awards for Latin American scientists to receive advanced research training in the United States, short-term exchange visits for U.S. and Latin American scientists for research and research training, and exploratory workshops to identify areas of mutual interest and develop plans for future research cooperation.

Cooperation With Eastern European and Soviet Scientific Communities. The recent political events in Eastern Europe and the U.S.S.R. have stirred interest in mutual broadening of scientific linkages. In response to these events, FIC developed an initiative that would expand on NIH's long history of cooperation with this region. Past collaborations covered such areas as cardiopulmonary disease, AIDS, environmental health, Lyme disease, sports medicine, eye diseases, maternal and child health epidemiology, orofacial and dental diseases, and primatology.

This initiative would build on existing mechanisms, such as exchange and fellowship programs and bilateral

agreements. Once additional resources are secured, they will support international research grant supplements for U.S. recipients of NIH awards, supplements to FIC's international epidemiology and postdoctoral AIDS programs, additional IRF's for Eastern European and Soviet scientists, and short-term exchange visits and technical conferences to identify areas of mutual scientific interest and future collaboration.

Policy Issues

FIC continually seeks ways to facilitate greater international collaboration for NIH and will continue to address issues such as increasing scientific opportunities with developing countries on behalf of the NIH community; strengthening research resources in the developing world while continuing to support cooperative research based on scientific excellence; strengthening FIC awards financially to attract the best scientific talent from around the world; creating budget flexibility to allow FIC to respond quickly to new international scientific opportunities; and developing strategies and options to implement FIC's program to provide international supplements to NIH grants.

National Center for Research Resources

Director's Preface

The National Center for Research Resources (NCRR) (formed by the merger of the Division of Research Resources with the Division of Research Services) supports the development of the research infrastructure necessary for Public Health Service (PHS)-supported biomedical and behavioral investigations. Thus NCRR is positioned best to address some of the most pressing issues facing NIH today: renovation and construction of research facilities; sophisticated instrumentation; care and use of research animals; development and use of nonmammalian models in research; and underrepresentation of minorities in biomedical research.

NIH's broad funding authority for construction, renovation, and replacement of health-related research facilities expired more than 20 years ago, and many of the buildings of the 1950's and 1960's have deteriorated and become obsolete. NCRR already assists biomedical research and educational institutions with alterations and renovations to upgrade laboratory animal facilities to meet the requirements of the PHS Policy on the Humane Care and Use of Laboratory Animals. Often, however, construction would be a more cost-effective way to comply with many new U.S. Department of Agriculture regulations on the care and housing of laboratory animals. In addition, existing facilities cannot always accommodate current needs for pathogen containment facilities, advanced technologies, and state-of-the-art instrumentation.

Advances in molecular biology, research on the human genome, neurobiology, structural biology, biotechnology, and acquired immunodeficiency syndrome (AIDS) research have come through the use of sophisticated and costly instrumentation resulting from the interdisciplinary collaboration of engineers, physicists, chemists, mathematicians, computer scientists, and biologists. Today's biomedical research requires the use of techniques and capabilities such as x-ray crystallography, computer-based image analysis, nuclear magnetic resonance (NMR) spectrometry, electron paramagnetic resonance imaging, computerized tomography, and molecular modeling. NCRR programs help provide sophisticated shared instrumentation to investigators, and establish and operate shared resources designed to foster collaboration and multidisciplinary research.

NCRR encourages proposals to develop research methods that do not require vertebrate animals and that reduce the number of vertebrate animals used, produce less pain and distress, and validate the reliability of current nonanimal methods and develop new ones. Recognizing that such research methods provide additional opportunities to advance understanding of biological processes, NCRR has established the Biological Models and Materials Resources Program (BMMRP) to address these issues.

To increase the number of minority scientists in biomedical research, NIH is attempting to encourage and recruit students into the biomedical sciences; these efforts are more effective when they start

with high school, and possibly even elementary school, students. Attention is also focused on the reduced life expectancy and higher prevalence of many serious diseases among minority Americans. Two NCRR programs address these issues: the Minority High School Student Research Apprentice Program (MHSSRAP) and the Research Centers in Minority Institutions Program (RCMIP).

Research Progress and Accomplishments

NCRR's programs have developed and maintained resources that have facilitated important accomplishments across the breadth of research conducted by the research institutes. The way NCRR's extramural programs work is exemplified by its support of research in 1989 on AIDS, Parkinson's disease, and cellular and molecular structure and function.

Acquired Immunodeficiency Syndrome. Fifty research facilities improvement applications for AIDS infrastructure were funded, 22 of these were for containment laboratories for the safe handling of the AIDS virus and 8 for animal facilities. Research activities requiring the new facilities included the evaluation of animal models for AIDS, basic virology research, and several pediatric outpatient clinics with associated laboratories for therapy evaluation studies.

More than 50 of the NCRR-supported General Clinical Research Centers host human immunodeficiency virus (HIV) research on the natural history of HIV-infected children and adults, and work to develop effective therapeutic approaches to combat opportunistic infections and strategies to restore or preserve immune function among HIV-infected patients.

A new beamline that can be used for x-ray diffraction studies of crystalline viruses and proteins from pathogenic sources was funded by NCRR's Biomedical Research Technology Program (BRTP) at the Cornell High Energy Synchrotron Source. This facility will be the only synchrotron facility in the world with a biological containment capability to permit structural studies of crystalline infectious agents such as polio virus and coat proteins from the AIDS virus and its receptors.

Investigators at a new center for the analysis of complex carbohydrates, funded by both NCRR and industry, recently completed analyzing the structures of the carbohydrates that coat the primary receptor for the AIDS virus. The carbohydrate coats on cells are the bases for antigenic activity, and the innovative techniques developed at this center should enhance the search for immunologic agents against the AIDS virus.

Recent studies by investigators at NCRR's Regional Primate Research Centers have confirmed that the simian immunodeficiency virus shares many characteristics with HIV. These findings have also led to the hypothesis that an African monkey virus may be the progenitor of both HIV-1 and HIV-2.

Funds from the Biomedical Research Support Grant Program (BRSGP) supported 117 small projects on AIDS, while the Shared Instrumentation Grant (SIG) Program supported 37 instruments that were used in 55 AIDS research projects.

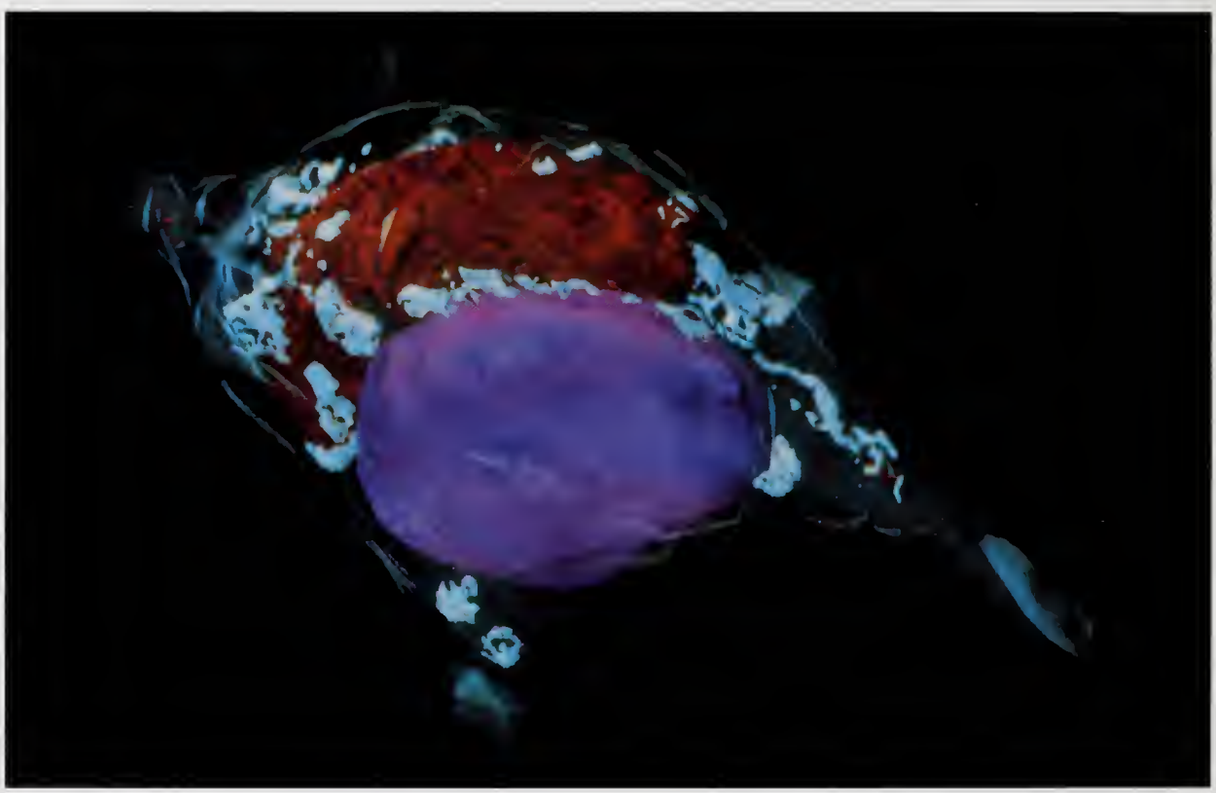
Parkinson's Disease. Research on Parkinson's disease demonstrates the importance of the range of NCRR-supported activities: clinical trials supported at General Clinical Research Centers revealed that the drug deprenyl delays the onset of disability in early, otherwise untreated Parkinson's disease; recent findings at Regional Primate Research Centers involved the reversal of some Parkinson's symptoms by transplantation of monkey fetal brain tissue. These advances offer valuable insights for possible moderation of the effects of this disease.

Cellular and Molecular Structure and Function. The importance of NCRR-supported technology was demonstrated

in a mass spectroscopy center by the determination of the chemical nature of the signaling mechanism used by bacteria to control the proteins involved in their motility. The basis for cellular motion responses is a major unsolved problem in cell biology; if this signaling mechanism proves to be widespread, it will have far-reaching implications for molecular interpretation of cellular behavior. NCRR's BMMRP supports the *Caenorhabditis* Genetics Center, which provides well-defined mutant strains of the nematode model. Because of its small size and defined embryonic lineage, this organism is a powerful experimental system: investigators studying cell-cell interactions have cloned *C. elegans* genes that mediate cellular interactions and have postulated the molecular function of these genes.

Future Research Opportunities

Animal Resources Program (ARP). ARP develops and supports animal resources and facilities for biomedical research, including animal models of human disease, postdoctoral training, and facilities improvement. The specialized facilities and environments of the seven Regional Primate Research Centers serve more than 1,300 biomedical researchers who use nonhuman primate models. The AIDS Animal Models Program supports breeding and research on chimpanzees and specific-pathogen-free colonies of rhesus monkeys for use in PHS-supported research on vaccine development and therapy measures for human AIDS. Animals produced by the Chimpanzee Breeding and Research Program will be available for important biomedical investigation, including AIDS and viral hepatitis. The immunologic and physiologic similarities of chimpanzees to humans make them essential for researching and testing candidate AIDS vaccines and evaluating the safety and efficacy of new drug therapies. ARP provides significant



This image of a nerve cell from a patient with Alzheimer's disease illustrates the dramatic progress that has been recently made in combining 3D graphics with structural information from electron microscopy. The image shows abnormal structures (large dark area in upper left—called paired helical filaments), which are associated with Alzheimer's disease.

assistance to research organizations that must upgrade and repair their laboratory animal housing and care facilities.

Biological Models and Materials Resources Program. Biomedical research will be most effectively advanced by the continuous application of a combination of mammalian and nonmammalian models. The BMMRP develops and supports nonmammalian models such as cell systems, lower organisms, and nonbiological systems as adjuncts to models that are phylogenetically more closely related to humans; it also provides critically important biological materials to the research community. BMMRP has initiated several NIH-wide program announcements to solicit applications on the development and use of model systems. With a firm commitment of support from NIH, NCRR's opportunity to expand knowledge by the use of these model systems will materialize.

Biomedical Research Support Grant Program. BRSGP strengthens the biomedical research infrastructure of PHS grantees by providing flexible funds on a formula basis for biomedical research needs not served by other programs. Funds are also provided for purposes best determined at the local level by grantee institutions, such as supporting the recruitment of young investigators and new faculty and helping to establish their laboratories, as well as supporting pilot projects to develop highly competitive grant applications. In addition to the aforementioned AIDS projects, 1989 BRSGP funds supported 270 projects for the mapping of human and complex genomes, supplied "bridge" funding to provide continuity to research projects that might otherwise have been terminated, supported shared core facilities such as tissue culture and hybridoma facilities, and upgraded animal facilities to achieve compliance with federal animal welfare regulations and PHS policy.

Shared Instrumentation Grant Program. The SIG Program helps institutions buy new instruments that cost more than $100,000. The maximum award is $400,000, and the equipment must be shared by three or more PHS-supported investigators. A wide variety of commercially available instruments, such as cell sorters, electron microscopes, and NMR and mass spectrometers, are supported. The growing need for instrumentation is reflected in the recent surge of applications. In both fiscal year (FY) 1989 and FY 1990, the SIG Program received more than 400 applications, nearly twice the number it received in 1982, its inaugural year.

Biomedical Research Technology Program. BRTP provides the scientific community access to centers staffed by gifted scientists and engineers at the forefront of their technological areas, to develop and apply new technological capabilities to cutting-edge biomedical research problems. At Carnegie Mellon University, BRTP is supporting the development of high-field superconducting magnet technology, which will make available a unique NMR spectrometer for biomedical studies at the highest achievable field. The instrument would be the first of its kind and would push the state of the art many years ahead of any commercially available instrument. Developments in high-field NMR will provide new basic research opportunities on biomacromolecules in solution, including detection of fast chemical exchange, molecular orientation and geometric structure, and the dynamics of interaction of biopolymers such as DNA with substrates, drugs, and toxins.

General Clinical Research Centers Program (GCRCP). The GCRCP provides clinical research infrastructure for approximately 7,250 investigators. The national network of 78 General Clinical Research Centers is essential for the conduct of clinical trials and other clinical research and supports the development

of future clinical investigators. The nature of clinical research has changed dramatically over the past several years. Progressively more complex outpatient research, requiring up to several hours per subject, is hosted across the centers. Studies incorporating new technology are ever more common, for example, sophisticated molecular biology techniques to define the genetic basis of disease and to develop therapeutic interventions based on recombinant DNA technology. In an era of relatively limited research funding, the GCRCP must work closely with NIH's categorical institutes to provide the most cost-effective clinical research and to assure that advances from sophisticated biomedical technologies are transferred to patient care. In addition, the GCRCP will provide resources to examine the causes of, and develop therapies for, disorders in underrepresented minorities and to develop minority clinicians into independent clinical investigators.

Minority High School Student Research Apprentice Program. The MHSSRAP provides minority teenagers an opportunity for hands-on experience in biomedical research. When it began in 1980, the program funded 200 students; in 1989 the number of apprentices was increased to 1,116. Because it has such a high priority, NIH institutes have agreed to provide additional funding for this program. In 1990, 2,144 students will be supported, and the 1991 appropriation request would support more than 5,000.

Research Facilities Improvement Program (RFIP). RFIP began in 1988 as a congressional initiative to fund the renovation and expansion of existing AIDS research facilities. The 1988 appropriation of $23.9 million was followed up with $4.9 million in 1989. This program has demonstrated an immediate and clearly pressing need for AIDS research facilities, as specifically addressed in the recommendations of the Presidential Commission on the Human Immunodeficiency Virus Epidemic.

Research Centers in Minority Institutions Program. In 1985, Congress mandated the RCMIP to expand the Nation's capacity for research in the health sciences by assisting predominantly minority institutions that offer the doctoral degree to improve their research infrastructure. Seventeen institutions have received awards, and five supplemental awards were made in FY 1989 to develop research infrastructure for AIDS and AIDS-related research. The expansion of the research capacity of RCMIP grantee institutions will enable them to become full participants in emerging biomedical research questions, especially in relation to minority populations. The RCMIP will play a major role in addressing diseases prevalent in minority populations and in working with minority populations on human genome-related questions. For example, a core immunogenetics laboratory supported by an RCMIP award is studying specific DNA sequences in relation to human leukocyte antigen (HLA) genotypes in various groups of patients with HLA-associated diseases, and the grantee intends to expand these activities to participate in human genome research.

NIH Publication No. 91-2912

January 1991