Science Advances for the FY 2001 OMB Submission

In the following pages, we highlight a number of advances that are representative of the many noteworthy accomplishments in medical research in the last year. Advances such as these hold promise for improving health and health care for all individuals.

Basic Research

A critical role for chromosome ends. An intriguing observation–that the ends of chromosomes (known as telomeres) progressively shorten as a human cell divides–has led scientists to wonder whether telomeres play a central role in the body's lifelong biologic clock. Telomere shortening has also been suggested to contribute to cancer, wrinkling and diminished skin elasticity, atherosclerosis, osteoporosis, a reduced capacity to respond to illness, and impaired cell division and specialization. New evidence from animal studies suggests that telomere shortening does indeed play an important role in the overall fitness of the aging organism. Scientists studied special mice lacking a protein responsible for maintaining telomeres at a constant length. The resultant shortening of the mouse telomeres was associated with shortened life span, reduced capacity to respond to physiological stresses, and increased cancer incidence.

Gene mutations linked to inflammatory diseases. An international team of researchers has discovered genetic mutations responsible for a newly recognized group of inherited inflammatory diseases. Patients experience dramatic, sometimes month-long episodes of high fever, skin rash, eye inflammation, and severe pain in the abdomen, chest, or joints. Some patients also develop a potentially fatal complication, called amyloidosis, that affects vital organs. Affected individuals from seven different families were found to have mutations in the gene for a protein known as the tumor necrosis factor (TNF) receptor. Normally the TNF receptor plays a role in the body's defenses against infectious and foreign agents. The mutated TNF receptors predispose patients to severe inflammation that can be triggered by daily life events such as emotional stress and minor trauma. Researchers are now testing the usefulness of synthetic forms of the TNF receptor in suppressing the inflammation. If successful, this would offer an important alternative to high doses of steroids (which can have serious side effects and are not completely effective) and could lead to the development of new treatments for many other immune-related and inflammatory disorders.

Versatile regulation of a cellular signaling protein. Gene regulation is essential in a variety of physiologic processes, including development and response to inflammatory and other environmental stimuli. The protein known as NF-kappaB has long been recognized as an important regulator of gene activity within immune and other cells. In order to carry out this function, this protein must be activated within a cell. Scientists now have determined that distinct pathways are involved in NF-kappaB activation following exposure to different environmental agents such as radiation or pro-inflammatory factors. Researchers have also discovered that one of the pathways leading to NF-kappaB activation plays an important role in limb development in mice.

New animal model of type 2 diabetes. Diabetes is one of the leading causes of death and disability in the United States, contributing to the deaths of more than 193,140 persons in 1996. There has been a need for development of an animal model for exploring how a defect in the insulin-response machinery within beta cells could lead to type 2 diabetes. Researchers funded by NIH have now developed a new animal model for studying type 2 diabetes. In this mouse model, the insulin-secreting beta cells of the pancreas cannot detect or respond to insulin. These mice develop a defect in the secretion of insulin that is very similar to that seen in type 2 diabetes in humans. This suggests that an inability of beta cells to detect and respond to the insulin that they secrete may underlie some aspects of type 2 diabetes.

Orange tonsils lead to new insights into cholesterol regulation. Just this month, researchers reported the discovery of a key gene involved in how the body regulates cholesterol. The gene, known as ABC1, encodes a protein that acts as a cellular pump, transporting high-density lipoprotein, or "good cholesterol," out of cells. The discovery arose out of an investigation of Tangier disease, a rare genetic condition characterized in part by inflamed, orange tonsils. Researchers determined that the orange tonsils were due to high levels of HDL cholesterol. After analyzing DNA samples from a few dozen patients from across the globe, the researchers learned that mutations in the ABC1 gene impair the cholesterol pump, causing a build-up of HDL cholesterol in cells. This discovery has important implications for atherosclerosis, a common disease in which the accumulation of cholesterol-filled cells along arterial walls leads to the formation of fatty plaques which eventually block blood flow. This research could contribute to the development of drugs that can regulate the cholesterol pump.

New clue to autoimmune diseases. Researchers recently identified a genetic mutation in immune cells that is responsible for the rare inherited disease known as autoimmune lymphoproliferative syndrome, or ALPS. Normally, once immune cells have protected the body from invaders such as bacteria and viruses, they "deactivate" by committing cellular suicide, a process known as apoptosis or programmed cell death. In ALPS patients, two particular types of activated immune cells are unable to commit suicide. One type, dendritic cells, are the activator of the other type, known as lymphocytes. As a result, lymphocyte immune cells remain activated, proliferate continuously, and attack the body. The underlying cause is mutations in a gene encoding a protein called caspase 10. Caspase was already known to be involved in apoptosis, but had never been linked to a human disease. The discovery of the role of caspase in the immune system and human disease lays a path for new ways to investigate autoimmune disease. More common autoimmune diseases such as diabetes, arthritis, multiple sclerosis, and lupus may also involve similar types of mechanisms.

Experimental malaria vaccine shows promise. A new candidate vaccine targeting several stages of the life cycle of the malaria parasite *Plasmodium falciparum* was shown to elicit a strong immune response in rabbits. The antibodies produced in response to the vaccine successfully recognized different developmental stages of the malaria parasite, blocked invasion of the parasite into the rabbits' liver cells, and inhibited growth of the organism in blood. The multi-target vaccine holds promise in providing protection against different stages of the

parasite's life cycle. Such multi-stage protection will be important for reducing the emergence of vaccine-resistant strains of the parasite.

Animal models offer clues to AIDS vaccine design and safety. An important step in the HIV vaccine development process involves defining the precise immune responses necessary to protect against infection with HIV. Several recent studies have provided important clues to this process. First, researchers demonstrated that "neutralizing" antibodies–capable of binding to a virus in a way that prevents it from infecting cells–are an effective protection against HIV infection in monkeys. These results suggest that an effective HIV vaccine might induce the production of neutralizing antibodies in humans. In another study using mice infected with an HIV-related virus, scientists have demonstrated that an immune response involving three types of immune cells provided more effective protection against infection than an immune response involving only one type of immune cell. This suggests that an effective HIV vaccine will also need to elicit a broad set of immune responses. In a third study, a live but weakened HIV-like virus was tested in monkeys as a candidate vaccine. It was hoped that this modified virus would produce a hearty immune response, providing protection against infection, but would not itself cause AIDS. However, the modified virus did cause AIDS in both infant and adult monkeys, suggesting that live-weakened HIV vaccines may also be unsafe. While progress has been made in our understanding of the requirements of for an effective HIV vaccine, further research is needed to help fill in pieces of the AIDS vaccine research puzzle.

Gene discoveries. In the past six months, NIH-supported investigators have discovered a number of genes that may play a role in serious diseases or important physiological processes, including:

- craniofacial malformations such as cleft lip and palate
- migration disorders and epilepsy
- hearing impairment
- Alzheimer's disease
- inherited inflammatory disorders, including Hibernian fever
- age-related macular degeneration
- sense of taste
- sense of smell
- biorhythm (day/night cycling)
- development of the hippocampus, a structure in the brain crucial for learning and memory

These new discoveries increase our understanding of both the role of genes in human health and disease and the mechanisms by which pathogens cause disease. This new information adds significantly to the knowledge base necessary for the development of new diagnostic, therapeutic and prevention modalities.

Clinical Trials

Successful ventilator strategy for ICU patients on life support. A large clinical trial of mechanical ventilator use for intensive care patients with acute respiratory distress syndrome was stopped early

so that critical care specialists could be alerted to the results. Data from the first 800 patients showed approximately 25 percent fewer deaths among those receiving small, rather than large, breaths of air from a mechanical ventilator. This is the first large clinical trial to demonstrate a superior approach to therapy for acute respiratory distress syndrome. The findings will improve the care of these patients and save thousands of lives each year. Acute respiratory distress syndrome is an often fatal inflammatory lung condition that usually occurs in conjunction with catastrophic conditions such as pneumonia, shock, sepsis, and trauma. Earlier studies had suggested that small breaths from the ventilator might not remove sufficient carbon dioxide, and that large breaths might damage lung tissue.

Combination treatment increases survival in advanced cervical cancer. Scientists continue to look for the most effective combination of treatments for devastating diseases such as cervical cancer. Recent results from each of five clinical trials showed an overall survival advantage for cervical cancer patients who receive cisplatin-based chemotherapy along with radiation therapy. The risk of death from cervical cancer was decreased by 30-50 percent by the combination of cisplatin-based chemotherapy with radiation therapy in women who required radiation therapy for treatment of cervical cancer. These results offer new hope to the nearly 14,000 women in the U.S. diagnosed with invasive cervical cancer each year.

Homocysteine and progression of arterial disease. A high blood level of homocysteine is an established risk factor for atherosclerotic coronary vascular disease, including coronary heart disease, cerebrovascular disease, and lower extremity occlusive disease. Previous studies have demonstrated that elevated homocysteine levels can be normalized or substantially reduced in most patients with the simple, inexpensive, oral administration of folate and vitamins B6 and B12. Researchers are now attempting to answer the logical question of whether vitamin treatment is beneficial in the prevention or treatment of atherosclerotic vascular disease. This evaluation, however, requires an understanding of the precise effect of homocysteine levels on the natural history of atherosclerotic disease progression. The first phase of a two-phase clinical study revealed that elevated blood levels of homocysteine are associated significantly with death, with death from cardiovascular disease, and with the progression of coronary heart disease in patients with symptomatic cerebrovascular disease or lower extremity occlusive disease. These results highlight the importance of clinical trials to test homocysteine-lowering vitamin therapy in such patients.

Applied Research

Simple, affordable method for preventing HIV infection in infants. Researchers have found a highly effective and safe drug regimen for preventing transmission of HIV from an infected mother to her newborn. The treatment is more affordable and practical than any other examined to date. A single dose of the antiretroviral drug nevirapine given to an HIV-infected woman in labor and another to her baby within three days of birth reduced the transmission rate by half, compared with a similar short course of the much more expensive drug AZT. If implemented widely in developing countries, this intervention potentially could prevent up to 400,000 newborns per year from beginning life infected with HIV.

Working artificial arteries grown in the laboratory. Researchers have developed for the first time a tissue engineering method to successfully grow functional arteries. The key was to take cells from adult pig arteries and grow them on a tube-shaped scaffold inside a bioreactor that mimicked the pulsing pressure encountered by a developing artery in the body. After about 8 weeks, the gross appearance and behavior of the vessels was similar to that of normal arteries. The vessels were then implanted into pigs where they appeared to function like normal arteries for close to a month. This finding has important implications for the development of future treatment of coronary heart disease.

New treatment of a complication of Crohn's disease. Crohn's disease is a chronic inflammatory bowel disease that is associated with the development of fistulas in approximately one third of patients. A fistula is an abnormal passage from an internal organ to the body surface or between two organs, is a serious complication of Crohn's disease, and is difficult to treat. Fistulas rarely heal spontaneously or respond to drug treatment and frequently require surgery. The local production of a chemical known as tumor necrosis factor α is thought to play a key role in the initiation and progression of Crohn's disease. Researchers previously reported that infliximab, a monoclonal antibody to tumor necrosis factor α, was effective in treating moderate-to-severe Crohn's disease. More recently, investigators demonstrated that infliximab is also an efficacious treatment for fistulas in patients with Crohn's disease.

National Institutes of Health
FY 2001 OMB Budget Submission

The Nation's investment in medical research supported and conducted by the National Institutes of Health (NIH) continues to lead to improvements in the health and the quality of life of individuals in this country and around the world. The generous budget increase in FY 1999 enabled the NIH to launch many new initiatives which have been continued in FY 2000. In FY 2001, we must sustain these efforts, seize additional scientific opportunities, and continue to respond to public health needs. The NIH will address four broad areas in FY 2001: exploiting genomic discoveries, reinvigorating clinical research, fostering interdisciplinary research, and working towards eliminating health disparities. Genomic studies are yielding data that can lead to new diagnostics, treatments, and prevention strategies. It is imperative that we have the appropriate mix of people and technologies to fully utilize the data and a strong clinical research infrastructure in order to translate it into new therapies and other interventions. In all of these efforts, there needs to be a special attention to health disparities associated with disease and disability.

Exploiting Genomic Discoveries

The Human Genome Project continues to generate information that is applicable to the development of novel medical treatments and prevention strategies. This model of national and international research and private and public collaboration is aimed at deciphering the DNA sequence of humans, that is, determining the exact order and composition of all the base units of DNA. Scientists across the Nation–supported by private industry, NIH, and the Department of Energy–and in Europe have already unraveled more than 20 percent of the human genome. They have also mapped more than 30,000 human genes (charted their relative locations on our chromosomes). There are probably another 50,000 genes still to be mapped and most of the human genome sequence remains to be determined. The Human Genome Project has successfully completed the pilot phase of sequencing the human genome which tested strategies and developed technologies for larger sequencing projects, and has launched the full scale effort to sequence all 3 billion bases of human DNA. The Project expects to produce at least 90 percent of the human genome sequence in "working draft" form by Spring 2000, considerably ahead of schedule. The working draft will then serve as the foundation for fine tuning the sequence–closing gaps and correcting errors–leading to completion of the permanent high-quality, human DNA sequence by 2003 at the latest.

Genomic research is not limited to the human organism. Studies are also underway to characterize the genetic blueprints of a number of disease-causing microbes as well as organisms that are used extensively in research laboratories as model systems. For example, the Mouse Genomic and Genetics Project is defining the structure of the entire mouse genome and is identifying the function of mouse genes by studying gene mutations. Resources will be used to develop core research centers and to train scientists to relate mouse pathology and physiology to the faulty genes. The end result will be new understanding of mammalian biology as well as new or improved "model systems" for learning about human diseases, genes, and proteins and for

testing new treatments. Ongoing and future research efforts will focus on the genomes of other important model organisms such as the rat, zebrafish, frog, fruit fly, slime mold, certain species of yeast and bacteria, and microorganisms that could pose a bioterrorism threat to our Nation.

Researchers use the maps and sequence data from model organism genomic projects such as these to help identify and locate genes involved in human disease. The increasing detail and quality of genome maps have reduced the time it takes to find a disease gene from years, to months, to weeks, to sometimes just days. Once a disease gene is identified, the next step is to determine the role it plays in human health and disease. With information from the Human Genome Project and other genomic studies, researchers can make these critical links rapidly, yielding a comprehensive picture of how our genes provide the instructions for the fundamental processes of life and laying the groundwork for the development of new and more effective diagnostics, treatments, and preventive strategies.

Genes direct the production of proteins, which are used as important structural components, for movement, in immune defense, and to carry out chemical reactions. Genomic discoveries often lead to new understanding of a protein's structure and function, which can in turn reveal new targets for drug development. For example, a drug might be designed to bind at a particular site on a protein so that it either corrects a problem in our cells or enhances the ability of the protein to perform an important task. Genetic information may also help identify individuals who will respond well or poorly to particular drugs. One of NIH's new pharmacogenetics initiatives is focused on the mechanisms underlying individual variations in drug responses. The ultimate goal is to understand how an individual's genetic makeup determines how effectively a medicine works in their body, as well as what side effects are likely to occur. Knowledge from this research will guide doctors in prescribing types and amounts of medications for a particular patient.

One of the most immediate clinical applications of genomic and genetic information is in the prevention and diagnosis of disease. Once it is established that a change, or mutation, in a gene is associated with a disease, a DNA test can be developed to identify its presence in individuals. Knowledge of increased susceptibility to a disease can then inform personal medical decisions.

Other genetic research focuses not on the entire genome, but on particular complex biological systems, processes, or diseases. The Brain Molecular Anatomy Project, for example, will continue to advance our understanding of the genes involved in brain and nervous system function in normal and disease conditions. Advances from this effort will aid in disease prevention, early detection, diagnosis, and treatment. Other genetic studies will concentrate on complex chronic diseases, such as diabetes and heart disease, and neurodegenerative disorders such as Alzheimer's and Parkinson's disease and retinal disorders. These diseases are particularly challenging because they result from the interactions of a number of genes and environmental factors. New understanding of the identity and interactions of key genes and environmental factors that contribute to disease will provide new targets for the development of therapeutic and prevention strategies.

Still other initiatives will address the genetics of development. For example, NIH will continue support of a facility for producing and characterizing laboratory mice harboring genetic mutations that affect development of the organism. Ultimately, studies using the mutant mice will be able to elucidate the cellular, molecular, and genetic mechanisms that direct development. Another program will identify the genes, genetic susceptibilities, and gene-environment interactions that contribute to human birth defects.

Fostering Interdisciplinary Research

The integration of abundant genomic information with findings generated from biochemistry and cell and developmental biology--and the translation of this information into new treatments, diagnostics, and prevention strategies--requires the collaboration of researchers from many disciplines. The contributions of mathematicians, physicists, engineers, chemists, and computer scientists are numerous and central to progress in modern biology and medicine. Recent advances and new technologies have increased our needs for collaborating with researchers in these disciplines and others and for training and supporting biomedical investigators in these varied disciplines.

The NIH will continue its efforts to encourage researchers in other fields to apply their skills and knowledge to biological and medical research. Examples of these efforts include issuing grant solicitations that invite applications from such investigators; supporting bioengineering research that integrates physical, chemical, or mathematical sciences and engineering principles for the study of biology, medicine, behavior, or health; continuing our investment in instrumentation development; participating in the President's Information Technology Initiative; constructing new beam lines for structural biology at Department of Energy's Synchrotron facilities; and developing interdisciplinary training programs and centers for drug development and other purposes.

Bioinformatics. Medical researchers are amassing enormous amounts of information today--from the Human Genome project, clinical trials, statistical studies, population genetics, and imaging research--thereby creating large repositories of information that far surpass all of the information collected previously. As the amount of data grows, the tools to compare and manipulate the data become more important and will be used to form bridges between databases to allow researchers to link disparate information sources. Critical to our efforts to analyze these data is the emerging field of bioinformatics that brings together cross-disciplinary expertise and technologies in biology, computer science, and mathematics. The focus of bioinformatics programs is on management of biological information that enables life science and novel therapeutic discovery to progress at a much faster pace. For example, the emerging field of pharmacogenomics will rely heavily upon the use of bioinformatics to integrate genomic information about populations and the response to therapeutic agents. Bioinformatic tools will be developed to integrate statistical genetic methods, gene sequence information, genetic variations in the populations, and epidemiologic data.

New technologies will be needed for information storage, manipulation, data encryption, and retrieval. In FY 2001, the NIH will support a new, interdisciplinary Biomedical Information Science and Technology Initiative (BISTI). As a component of BISTI, National Programs of Excellence in Biomedical Computing Support will be established as a means for learning at the interfaces of biology, mathematics, and computation. Also as a part of BISTI, NIH will develop a series of biocomputing centers that will be based at universities and research centers. In addition to the need to develop new tools and technologies to handle the increasing amount of data, there is a major, worldwide need for trained bioinformatics specialists to address these emerging research challenges. NIH will be developing cross-disciplinary educational programs to help ensure that a stable workforce is in place.

Reinvigorating Clinical Research

A strong and stable clinical research enterprise is a prerequisite for continued progress in translating medical research into practice. NIH's centers for clinical research, including the General Clinical Research Centers (GCRCs), provide an important bridge for extending discoveries from the laboratory bench to application in patients. In FY 2001, NIH will increase its support of GCRC programs for clinical evaluations of diagnostic technologies, as well as therapeutic and prevention interventions for a broad range of acute and chronic diseases and conditions.

New networks for clinical research and clinical trials will be needed to examine innovative therapies for cancer, stroke, diabetes, kidney and urinary tract disorders, and mental health disorders. Additional clinical trials are needed to translate findings from basic science into improved diagnostics and therapeutics. For example, to help speed development of new cancer therapeutics, the Rapid Access to Intervention Development (RAID) program makes available to the academic research community resources—products and information–for the pre-clinical development of drugs and biologics. The goal of RAID is clinical "proof of principle" that a new molecule or approach is a viable candidate for expanded clinical evaluation.

New technologies are enabling production of large numbers of new chemical entities to be evaluated as target-specific candidate therapies. Improved safety evaluation methods are needed to provide preclinical and clinical testing in an efficient and timely fashion. The use of biological markers, or biomarkers, defined as characteristics that can be measured and evaluated as indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention, is one approach to enhance testing of new chemical entities. Biomarker research programs for cancer, Parkinson's disease, stroke, arthritis, and other chronic diseases will help streamline the development and clinical testing of new treatments, thereby enabling patients with these disorders to benefit more quickly from laboratory discoveries. In addition, the NIH Center for Complementary and Alternative Medicine will support rigorous and high quality clinical research on complementary and alternative medicine practices and disseminate information to practitioners and the public.

For clinical research to succeed as part of the biomedical research enterprise, increased efforts to revitalize the clinical investigator workforce are needed. Changes in the health care delivery

system have eroded the clinical research infrastructure. Sustaining and replenishing this environment to meet future needs requires multiple approaches to address this complex problem. In FY 2001, NIH will continue to invest in successful new training and research support programs for clinical trainees and their mentors. Additional support will be directed to a clinical research curriculum development program that, by FY 2001, will be flourishing in many of the Nation's academic institutions. Other approaches to stimulate career development of clinical investigators will be implemented. Analyses have shown that debt incurred by years of medical training is a major deterrent for the pursuit of clinical research careers by health professionals. Consistent with the recommendations of the NIH Director's Clinical Research Panel, an extramural clinical research loan repayment program will be developed to help recruit and retain clinical researchers. Clinical research training on the NIH campus will be enhanced to attract medical and dental students to cutting edge clinical research. Education models for clinical research will be fostered, such as the Clinical Center Grand Rounds, which are being telecast to over 50 medical schools and over 1000 medical centers nationwide.

Concurrent with an expanded clinical trials program, NIH is improving data systems to increase patient access to information about these trials. The NIH is establishing a "one-stop shopping" registry of clinical trials for serious and life-threatening diseases or conditions, as mandated by the Food and Drug Administration Modernization Act of 1997. This national resource will include information about the purpose of each trial, eligibility criteria, location of the trial site(s), and point of contact for further information about the trial. Efforts will also be initiated to make available the information in the database through a toll-free telephone number and other communications mechanisms.

Working with the managed care industry, NIH is trying to foster collaboration between managed care organizations and researchers and to broaden the access of managed care subscribers to clinical trials. The NIH will continue to work with the American Association of Health Plans in implementing their joint agreement to promote access to clinical trials and payment by health plans of routine patient care costs associated with participation in clinical trials. This is an important, albeit first, step towards increasing patient access to clinical trials.

Working Toward Eliminating Health Disparities

Disparities in health may be due to socioeconomic status; racial, ethnic, and cultural factors; gender; and the environment. For example, Americans born into minority racial and ethnic groups face disproportionately high infant mortality, low rates of childhood vaccination, high prevalence of cardiovascular disease and diabetes, and shorter life spans than does the population as a whole. Health disparities cross national borders as well, especially between developed and developing regions of the world. Malaria, AIDS, and tuberculosis are just a few of the diseases that pose particular burdens for developing countries.

A key component of the nation's strategy to eliminate health disparities is basic, clinical, translational, health services, and community-based research. Included are studies to determine reasons for health disparities associated with differences in culture, language, diet, nutrition,

physical activity, socioeconomic and demographic status, gender, age, environmental pollutants, and occupational hazards; to identify risk factors for disease among different populations; and to develop prevention strategies and other interventions for these populations.

Enhanced support for research, research training, and infrastructure needs will accelerate the generation of new knowledge about health disparities. In this regard, in FY 2001, the NIH will begin support of Centers of Excellence for Research on Health Disparities. These centers will encompass basic and clinical research focused on addressing health disparities, particularly those affecting minority and disadvantaged socioeconomic groups. Major goals of these centers will be to establish, strengthen, and expand research and training on health disparities; to enhance the academic performance of minority students; to increase the number and quality of minority applicants for research grants; and to improve the capacity to train, recruit, and retain minority faculty.

In addition to research conducted through the centers, NIH will continue to support a broad range of research, including studies of how socioeconomic and cultural factors contribute to the development of health beliefs and practices, expanded efforts in population genetics, and efforts to gain a more fundamental understanding of the effects of the environment, culture, and economic status on health. Research will also continue to address health disparities with respect to various diseases. For example, the magnitude of the AIDS pandemic is profound. AIDS has significantly lowered the life expectancy in many nations of Africa, the global epicenter of AIDS. There has been a steep increase of new infections in Sub-Saharan Africa, and burgeoning disease rates also threaten the vast populations of India, Southeast Asia, and China. In the United States, new HIV infections and AIDS-related deaths continue to increase in many subpopulations–among women, racial and ethnic minorities, heterosexuals, adolescents, drug users, and people over 50 years of age. NIH research in this area will include examining gender differences in HIV/AIDS, disparities in response to therapy and prevention among minorities, and clinical trials and research infrastructure development to facilitate the conduct of international studies. In addition, NIH's Vaccine Research Center (VRC) is focusing on the development of candidate vaccines against AIDS, and is stimulating multidisciplinary research, from basic and clinical immunology and virology through vaccine design and production.

Large differences exist across, ethnic, racial, and gender groups in access to care for mental illness, in understanding of mental health, in treatment seeking behavior, and in the prevalence of some forms of mental illness. Research on mental illness and mental health will continue to range from the laboratory bench to the treatment clinic, including translating state-of-the-art scientific knowledge to community-based practice. Major areas for study include the effects of culture on mental disorders, the economic and social barriers to diagnosis and treatment, how gender differences influence the development and course of mental disorders, and the behavioral and cognitive effects of environmental exposures on children.

FY 2000 BUDGET POLICY

The FY 2000 President's Budget of $15,933 million for the NIH, provides a total increase in budget authority of $336 million or 2.2 percent over the FY 1999 Enacted level. Targeted areas

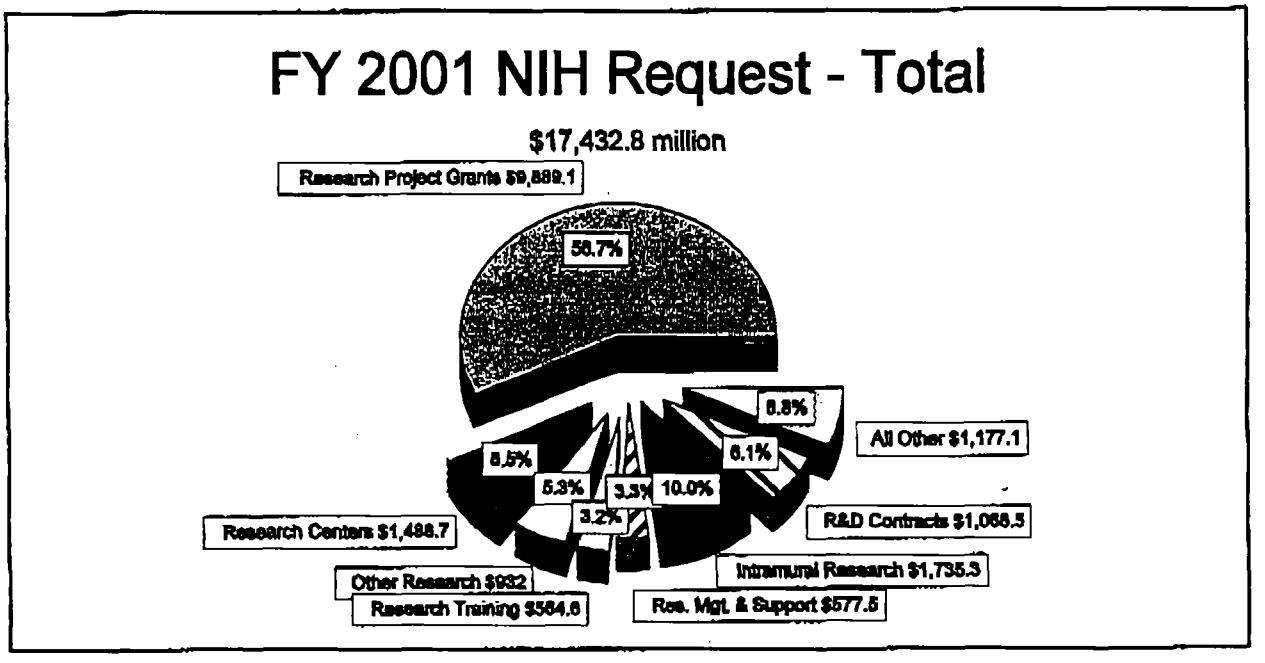
of emphasis were: Biology of Brain Disorders; New Approaches to Pathogenesis; New Avenues for Development of Therapeutics; New Preventive Strategies Against Disease; Genetic Medicine; Health Disparities; and Bioengineering, Computers and Advanced Instrumentation.

FY 2001 BUDGET POLICY

The FY 2001 request to OMB provides $17,433 million for NIH, an increase of $1,500 million or 9.4 percent over the FY 2000 President's Budget. The AIDS research program would increase by approximately the same percent as the NIH increase for research supported through Institutes and Centers (ICs).

In FY 2001, the NIH will continue to generate new scientific knowledge and develop new treatments and new prevention strategies for the score of diseases and disabilities which affect the public's health. The NIH will make use of its research capacity by continuing the many activities initiated in FY 1999 and FY 2000 and pursuing selected new initiatives. These scientific efforts can be characterized by four cross-cutting research themes: the exploitation of genomic discoveries; interdisciplinary research; the reinvigoration of clinical research; and the elimination of health disparities.

New strategies for the prevention and treatment of disease, never before thought possible, are within our reach. These extraordinary scientific opportunities challenge the NIH to find new mechanisms and new programs to maintain the pace of scientific discovery. Increasingly,



researchers spend relatively more time on computations. NIH must find ways to discover, encourage, train, and support the new kinds of scientists needed for tomorrow's science. The FY 2001 request to OMB includes $66.7 million for Biomedical Information Science and

Technology Initiative (BISTI) to begin the first steps in meeting this need. This will be a trans-NIH initiative encompassing several mechanisms of research support: research project grants (RPGs) for interdisciplinary grants in bioinformatics ($11.4 million), research centers, for National Programs of Excellence in Biomedical Computing Support ($47.8 million), National Research Service Awards (NRSAs) to begin training a new generation of researchers with cross-disciplinary skills, ($3.2 million) and the Library of Medicine, for development of informatics and molecular computational biology projects ($4.0 million), as well as a small project in Intramural Research ($0.3 million).

The NIH fully supports several Secretarial Initiatives, including a collaboration with the Substance Abuse and Mental Health Services Administration (SAMHSA) to develop a new initiative on Mental Health in the FY 2001 budget submission. This initiative, for which NIH"s portion is an increase of $99.7 million, will integrate research and prevention strategies with actions designed to improve the delivery of mental health services. Special emphasis will be placed on public health issues relating to the mental health of adolescents, minorities, and the aged, and of individuals with multiple diagnoses, including drug and mental disorders.

The NIH will support $33.6 million in research related to the Bioterrorism Initiative, an increase of $4.4 million, or 15 percent, over the FY 2000 President's Budget. Effective strategies for dealing with bioterrorism agents require rapid diagnostic and treatment abilities as well as bioprotective vaccines. These efforts will require multidisciplinary expertise, including microbiology, immunology, genetics, chemistry, bioengineering, and computer science. New funds will be used to sequence and analyze the genomes of potential bioterrorism agents. This information will be applied to develop methods for rapidly detecting and identifying natural and bioengineered pathogens and to devise tests for rapidly determining a microbe's sensitivity to drug therapy. Additional funding will also be used to accelerate the development and testing of new drugs and vaccines against bioterrorism organisms. Analytical technologies such as mass spectroscopy will be explored for their application in identifying chemicals and toxins that pose a threat to the Nation.

The FY 2001 request to OMB provides $756.1 million to support to the Secretary's Disease Prevention and Health Promotion initiative, by sponsoring research directed toward furthering the understanding of why people engage in healthy or risky behavior and developing and testing preventive interventions at the individual and community level. NIH also supports the Secretary's FY 2001 Asthma Initiative by requesting a total budget of $130.6 million, an increase of $12.7 million over the FY 2000 President's Budget. NIH will support new research initiatives such as adult onset of asthma, prevalence of asthma in special populations, asthma severity during pregnancy, and additional education/outreach activities, as well as launching an Inner-City Asthma Study.

The NIH is supporting the Secretarial Initiative in Health Disparities. One exciting new program planned for FY 2001 is the creation of Centers of Excellence for Research on Health Disparities and Training in the Office of the Director, which will provide research grants and contracts for researchers in health disparities and education and training for minorities and other

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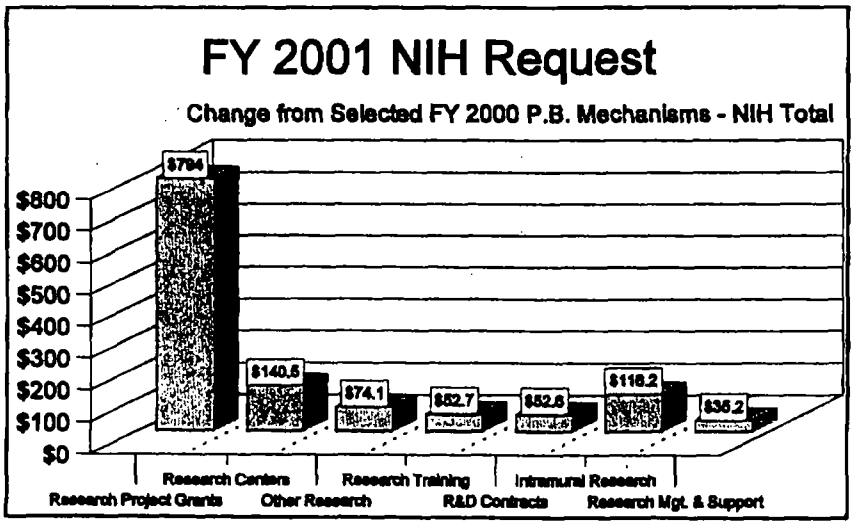
disadvantaged socioeconomic groups. NIH is proposing that $20 million be devoted to these new Centers of Excellence in FY 2001.

The NIH has developed a plan to further research in pandemic flu. In addition to supporting a grants and contract program in basic biology, epidemiology, vaccine development and evaluation, drug discovery, development and evaluation, and diagnostics, as related to influenza, funds requested in FY 2001 will allow the initiation of the production of an inactivated, live attenuated, and/or recombinant vaccine against a single avian influenza virus subtype of high pandemic potential. NIH estimates that $18.1 million would be spent on influenza research in FY 2001.



Funding medical research through investigator-initiated grants continues to be one of the highest priority of NIH. NIH would fund a total of 7,868 competing RPGs in FY 2001 for $2,342.9 million, an increase of 251 competing grants over the FY 2000 President's Budget. Funding for noncompeting commitments will increase by $669.7 million for a total of $7,103.4 million. NIH will pay as close to recommended levels as possible for competing RPG awards. An increase of 5 percent on average for competing RPGs will allow NIH to make continued progress towards this goal. The apparent lack of increase in average costs for total competing RPGs from FY 2000 to FY 2001 results from the cycling of the unusually expensive Adult Therapeutic Clinical Trial Network for AIDS grants, as well as the HIV Vaccine Leadership Group and Network and HIV Prevention Leadership Group and Network grants, from competing to noncompeting status in FY 2001. Adjustments to exclude these grants from the base for competing RPGs in FY 2000 results in an average cost for competing RPGs of approximately 5 percent over FY 2000. Noncompeting RPGs will be funded at committed levels. Recurring direct costs for individual noncompeting RPGs will increase by 3 percent on average over FY 2000 costs.

In the FY 2001 request to OMB, support for centers programs would total $1,488.7 million. This includes $47.8 million to fund new BISTI centers at $3 to $5 million each. Research Centers in Minority Institutions would increase by nearly 11 percent to $41 million. Within Other Research

new diseases

NATIONAL INSTITUTES OF HEALTH

($ in millions)

	1998	1999	2000	2001	2002	2003
FY 1999 Original Path (+48% over 5)	**13,622**	**14,763**	**15,661**	**16,632**	**17,997**	**20,188**
Increases vs FY98		1,141	2,039	3,010	4,375	6,566
% Increase vs FY98		8.4%	15.0%	22.1%	32.1%	48.2%
FY 2001 Budget (using "updated" 1999 Path)	**13,622**	**15,607**	**17,813**	**18,813.47**	**19,501**	**20,188**
Increases vs FY98		1,984	4,191	5,191	5,878	6,566
% Increase vs FY98		14.6%	30.8%	38.1%	43.2%	48.2%
"Doubling over 5"	**13,622**	**15,607**	**17,813**	**18,813.47**	**23,029**	**27,245**
Increases vs FY98		1,984	4,191	5,191	9,407	13,622
% Increase vs FY98		14.6%	30.8%	38.1%	69.1%	100.0%

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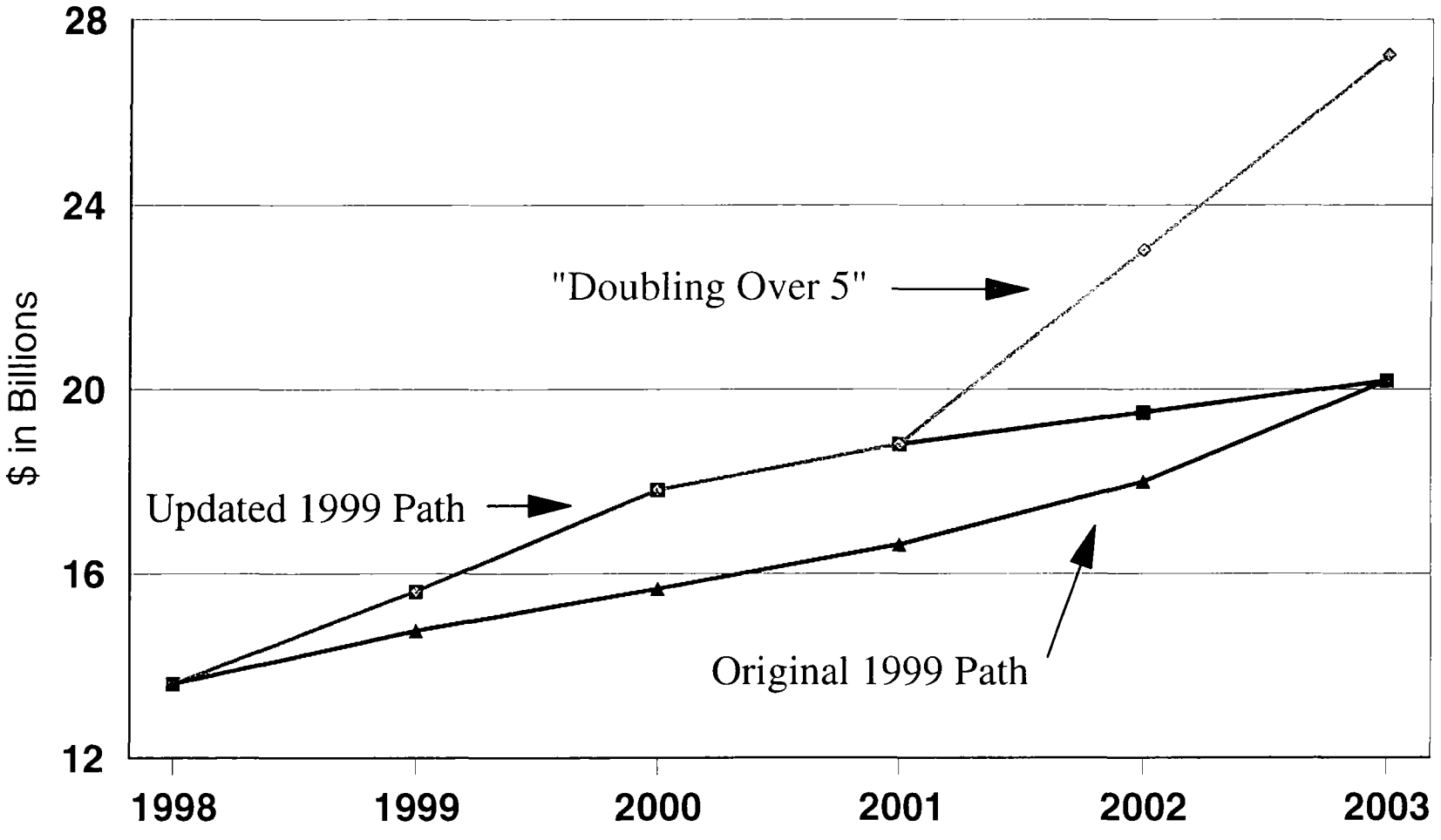
Doubling NIH's Budget over FY 1998 Levels Would Require Two Years of $4 billion Increases in FY 2002 & 2003*



* Assumes $1 billion Increase in FY 2001; does not address years beyond FY 2003