INTRODUCTION

The nation's substantial investment in the NIH is yielding myriad scientific achievements, many of which are improving the length and quality of human life. Research is contributing to the dramatic reduction in mortality from heart disease and stroke. Cancer incidence and death rates are declining. Furthermore, we are improving our capacity to rapidly control new infectious diseases soon after they emerge. The research NIH conducts and supports today will be the basis for countless future advances in science and improvements in health. One of the most visible examples, the completion of the sequencing of the human genome, is creating previously un-imagined opportunities for more precise prediction of susceptibility to disease, response to medication, and development of new preventive and therapeutic approaches.

Chronic diseases now account for 70 percent of all deaths and 75 percent of today's health expenditures. Ironically, the rise in the incidence and prevalence of chronic disease is the result of the Nation's success in battling acute and lethal diseases - a success that also led to a significantly higher life expectancy. But, as the share of the U.S. population over the age of 65 increases, so has the segment of the population most likely to suffer from chronic diseases such as cardiovascular disease, Parkinson's disease, diabetes, obesity, Alzheimer's disease, hypertension, and cancer. In addition, as the agency increases its focus on chronic diseases, infectious diseases remain a continuing and evolving challenge. NIH is sustaining its commitment to address infectious diseases, including new infections, such as SARS; re-emerging/resurging infections, such as influenza and antibiotic resistant tuberculosis; and bioterrorism, the deliberate release of pathogens. Moreover, NIH remains focused on eliminating health disparities among racial, ethnic, and disadvantaged populations and on addressing the special health needs of individuals at all stages of life—from the newborn to the elderly.

NIH is vigorously implementing the NIH Roadmap for Medical Research. Launched in September 2003, the NIH Roadmap is a set of initiatives responding to emerging scientific needs and opportunities that do not fit clearly within the mission of a single or a small group of Institutes and Centers (ICs), but that require substantial attention in order to take advantage of current opportunities in science. Planned initiatives under the Roadmap are described starting on the next page of the overview.

NIH-funded programs are unique in both igniting and complementing private sector research and development efforts. NIH tackles studies for which the risks are too high, or the fiscal incentives too low, to attract private investment. These research arenas span the health care spectrum, ranging from basic studies and technology development to the commercially impractical, yet critical, evaluation of lifestyle interventions such as modified diet and exercise. Tailoring therapies for the special needs of vulnerable populations and evaluating treatments for rare diseases are other areas of NIH investigation where the intervention of a public agency is essential. With the massive responsibility of advancing knowledge across such a wide landscape, whenever possible, NIH marshals efforts of industry, research organizations, disease

foundations, and patient groups to maximize its efforts. To maintain the vibrancy of our nation's scientific enterprise, NIH actively supports strong basic and clinical research training programs.

NIH ROADMAP FOR MEDICAL RESEARCH

Launched in September 2003, following over a year of intensive planning, this is a set of initiatives jointly planned and executed by all ICs, with specific plans extending from FY 2004 to FY 2009. The NIH Roadmap for Medical Research is a set of trans-NIH research initiatives that are designed to accelerate the pace of discovery and improve the translation of research findings into medical and health interventions for public benefit. The Roadmap was purposefully focused on efforts that no single or small group of Institutes or Centers could or should conduct on its own, but that NIH as a whole must address to ensure both efficient and effective discovery. The initiatives selected for funding met these criteria: they are transforming, that is, they will dramatically change the content or the process of medical research in the next decade; the outcomes from the initiative will be used by, and synergize the work of, many Institutes; the initiatives are compelling to NIH stakeholders; and the initiatives position the NIH to do something that no other entity can or will do.

The seeds of this effort began in 2002 with input from over 300 stakeholders representing academia, industry, government and the public. Based on that input, subsequent NIH leadership discussion, and the deliberations of working groups, NIH developed a vision for a more efficient and productive system of medical research, a framework of priorities that the NIH must address in order to optimize its entire research portfolio, and a set of initiatives for implementing the vision and priorities. The initiatives focus on major opportunities and gaps in the research agenda that no single or small group of institutes can tackle alone, but that the agency as a whole must address.

The Roadmap has three themes - New Pathways to Discovery, Research Teams of the Future, and Re-engineering the Clinical Research Enterprise - comprising 28 trans-NIH research initiatives. NIH began implementing the initiatives in FY 2004. Initiatives that build upon existing research efforts are expected to achieve their goals rapidly, while other newer, or more complex, endeavors will likely take years to come to fruition. Examples of the initiatives are highlighted below.

New Pathways to Discovery

As witnessed with the sequencing of the human genome, addressing some of the most complex gaps in biomedical science provides scientists with new tools, new ideas, and even new disciplines with which to solve public health problems. Initiatives under the NIH Roadmap's *New Pathways to Discovery* theme seek to identify and study complex networks of cellular machinery at the levels of proteins, metabolites (lipids, carbohydrates, amino acids), and molecules, as well as at the even smaller level of atoms.

Molecular Libraries and Imaging. Small organic molecules have proven to be extremely useful research tools, or "probes," to study gene function, cellular pathways, and other aspects of basic biology. However, it is necessary to screen thousands of small molecules in order to determine their utility as a research tool, and public-sector scientists have only limited access to advanced

screening facilities. The Molecular Libraries and Imaging Initiative will establish screening centers to identify and characterize the properties of useful small molecules, create and maintain a national repository of such molecules, and make all data and compounds available to the public. Scientists can then use these molecules as tools to facilitate studies of basic biological mechanisms. An increased understanding of these mechanisms may ultimately lead to new therapies. In addition, the development of imaging technologies and reagents will permit investigations of cell and tissue function at the molecular level. Selected Molecular Libraries and Imaging components are described below:

< Molecular Libraries Small Molecule Repository. The Small Molecule Repository will acquire, maintain, and distribute a collection of up to 500,000 small-molecule compounds with diverse chemical structures and biological activities. The repository will provide these compounds to the Molecular Libraries Screening Centers Network for use in high-throughput screening. Molecules found to have useful activity can be employed by the scientific community as biological probes for the study of molecular and cellular pathways. These compounds will be made broadly available to scientists through the Repository. The chemical structures of the compounds in the repository, along with the associated screening data, will be shared with the public through the newly created database PubChem (http://pubchem.ncbi.nlm.nih.gov). The Repository will be expanded in FY 2005 by the addition of two new grant programs in chemical diversity.

< *Molecular Libraries Screening Centers Network.* The Molecular Libraries Screening Centers Network will be a national resource to empower scientists to explore biology using small molecules. The Network will use biological assays submitted by the research community to screen large numbers of molecules maintained by the NIH Small Molecule Repository and will optimize these molecules so they are most useful. The NIH Chemical Genomics Center, established in FY 2004, is the first of the molecular libraries screening centers to be established, and it is beginning to perform assays for the extramural and intramural research communities. The remaining centers in the initial network will be funded through a three-year pilot program beginning in FY 2005.

< *PubChem.* To help researchers link small molecules to their biological functions and to the macromolecules with which they interact, NIH has created the PubChem suite of databases. Moreover, the PubChem databases have been integrated within the network of over 20 other biological databases. With this new resource, developed under the umbrella of the NIH Roadmap for Medical Research, for the first time, researchers have the unprecedented opportunity to view small molecules in a broad biological context. Ultimately, as it acquires the massive amounts of data it is designed to capture, PubChem will be an essential tool for unraveling the complex web of metabolic interactions and signaling pathways that allows cells to function.

< In FY 2006, NIH will reissue the *High-Throughput Molecular Screening Assay Development* solicitation and will issue a new solicitation - *Novel Preclinical Tools for Predictive ADME-Toxicology*. The latter solicitation aims to improve methods used to test compounds for various properties including absorption, distribution, metabolism, excretion (ADME), and

toxicity. Better ability to predict the profile of chemical compounds in clinical testing will prevent some of the trial-and-error in clinical testing.

< *Molecular Imaging Probes:* Molecular imaging is an emerging research area aimed at imaging specific molecular pathways in living tissues and cells, particularly those that are key targets in disease processes. Unlike anatomical imaging, molecular imaging displays the biochemical and physiological abnormalities that underlie disease, rather than simply the consequences of these abnormalities. Thus far, however, molecular imaging methods have been limited by the poor sensitivity and specificity of currently used molecular probes. The Innovation in Molecular Imaging Probes initiative will encourage the development of new probes that will dramatically improve the ability to detect and image specific molecular events. The new probes may also have potential for clinical applications.

< Also in FY 2006, the *NIH Imaging Probe Development Center,* implemented within the intramural research program, will be fully operational and will begin servicing the extramural research community. This center, designed to interact with other Molecular Libraries and Imaging Roadmap initiatives, will generate novel imaging probes and produce "known" or published imaging probes for which there is no commercial supply.

Highlights of other Roadmap initiatives under the theme, New Pathways to Discovery, are presented below.

< *National Technology Centers for Networks and Pathways.* The focus of these centers is on tool development for measuring protein activity and interactions. Two Centers have been funded to investigate the array of intricate and interconnected pathways that enable communication among genes, molecules, and cells. Researchers at the Centers will discover many more pathways, decipher how pathways are integrated in humans and other complex organisms, determine how disturbances in pathways lead to disease, and learn what might be done to restore disturbed pathways to their normal functions. Additional centers will be funded in 2005.

< *Standards and Critical Reagents for Proteomics.* Proteomics is the systematic study of proteins and their complex interactions in a cell or organism. Because proteomics is a new and complex scientific field, it is crucial to establish standards that will enable proteomic data from different laboratories to be easily shared, compared, and evaluated. FY 2006 initiatives will support research to establish needed standards and develop new statistical methods and software for analysis of proteomic data and evaluation of the quality of these data. New chemical agents (reagents) will also be critical for proteomic research, and NIH is planning to support the development of new technologies to produce such reagents.

< *National Centers for Biomedical Computing.* Because the science of information management has become an integral element of scientific investigation, and to meet the infrastructure needs of modern research, the NIH is embarking on a long-term initiative to establish an integrated national biomedical-computing environment. Four Centers have been funded to develop software programs and other tools to analyze, integrate, visualize, and model large volumes of biological data. Additional centers will be funded in FY 2005. The

Centers also will play a major role in educating and training researchers to engage in biomedical computing and provide the tools for researchers to seamlessly share data from large experiments performed at multiple sites.

< *Nanomedicine Centers.* Nanomedicine refers to medical intervention at the molecular level to cure disease or repair tissue such as bone, muscle, or nerves. Twenty Nanomedicine Concept Development Awards have been funded to plan the content, structure, and funding strategies for formal nanomedicine centers. The best features of these plans will be used to develop a solicitation for Nanomedicine Development Centers, envisioned to be staffed by multidisciplinary teams comprised of biologists, physicists, biochemists, mathematicians, engineers, computer scientists, and others. The first Nanomedicine Development Centers will be funded in FY 2005. Additional Centers will be funded in FY 2006.

Research Teams of the Future

The scale and complexity of today's biomedical research problems require today's researchers to intellectually extend themselves beyond their own areas of research to create new collaborative science teams and new scientific disciplines. *Research Teams of the Future* encourages new ways of combining skills and disciplines in the physical, biological, and social sciences; the training of investigators; and the development of novel support mechanisms to facilitate these endeavors.

< *Exploratory Centers for Interdisciplinary Research.* NIH funded 21 planning centers in FY 2004 that combine various aspects of individual disciplines to conceive new ways of approaching central, complex problems in the biomedical sciences. Teams of investigators are planning approaches for the creation of new biomedical and behavioral interdisciplinary fields in order to yield insights that could not have been achieved by an isolated laboratory or using a multi-disciplinary approach. The exploratory centers are intended to lay the foundation for submitting subsequent applications for Interdisciplinary Research Consortia.

< In FY 2006, NIH will hold a conference on the analytic strategies necessary for the integration of the behavioral and social sciences with biomedical, computational, physical and engineering sciences. This conference, the *Interdisciplinary Technology and Methods Summit,* will focus on topics such as pain, fatigue and obesity that are in need of an interdisciplinary approach that integrates the behavioral, social and biomedical sciences.

< *Interdisciplinary Research Training.* A critical aspect of developing the capability to perform interdisciplinary research is training of scientists at all career stages. A number of interdisciplinary training activities have been funded including:

> *Training for a New Interdisciplinary Research Workforce.* This supports novel programs at the undergraduate through postdoctoral levels that will foster the development of a core of research scientists able to apply interdisciplinary solutions to complex biomedical and health problems.

> *The Curriculum Development Award in Interdisciplinary Research.* This funds grants to develop innovative courses, curricula, and approaches in integrated biomedical, behavioral, and quantitative science areas.

> *Interdisciplinary Health Research Training in Behavior, Environment, and Biology.* This funds programs to provide formal coursework and research training in new interdisciplinary fields to individuals holding advanced degrees.

< *Interagency Conference on the Interface of Life Sciences and Physical Sciences.* In November 2004, NIH and the National Science Foundation held the "Conference on Research at the Interface of the Life and Physical Sciences: Bridging the Sciences." The conference was co-sponsored with other Federal agencies including the Department of Energy, Defense Advanced Research Projects Agency, National Aeronautics and Space Administration, National Oceanic and Atmospheric Administration, National Institute of Standards and Technology, Environmental Protection Agency, and others. The overall objective of the conference was to obtain input on how to spur cross-fertilization to prompt breakthroughs in both areas and to facilitate collaborations between the fields. A conference report and recommendations will be forthcoming.

< *NIH Director's Pioneer Award.* Accelerating the pace of discovery requires novel mechanisms of research support that encourage risk-taking. The newly established NIH Director's Pioneer Awards program is designed to encourage investigators to pursue innovative, unexplored avenues of research that are high risk but have the potential to result in truly groundbreaking discoveries. Traditionally, NIH supports research projects, not individual scientists. However, this award mechanism will enable NIH to support a highly select group of individuals who have the potential to make extraordinary contributions to medical research. In FY 2004, NIH funded nine scientists, who were evaluated by an external panel, for their ability to integrate diverse sources of information, an inclination to challenge paradigms and take intellectual risks, diligence and concentration necessary to plan and execute effective strategies for accomplishing goals, and prospects for making seminal biomedical research advances. In FY 2006, the NIH Director's Pioneer Awards program will be in its third cycle.

Re-engineering the Clinical Research Enterprise

To capitalize on the revolutionary discoveries emerging from basic science, there is a pressing need to strengthen and accelerate the clinical research process and to more efficiently transmit research findings to practitioners on the front lines. NIH Roadmap initiatives will incorporate modern information technology; promote improved integration of clinical research networks; stimulate the development of more effective means to assess pain, fatigue, and other subjective clinical outcomes; facilitate the coordination of clinical research policies; improve clinical research workforce training; and support key elements of the translational research infrastructure.

< *Integrating Clinical Research Networks and Enhancing Informatics.* To promote and expand electronic clinical research networks, feasibility studies are underway to identify best practices in existing networks and to test concepts for enhancing network interoperability and

capacity. An inventory will characterize extant network informatics infrastructure. Results from these studies will shape development of the National Electronics Clinical Trials and Research Network (NECTAR), the informatics infrastructure that will serve as the backbone for interconnected and inter-operable national research networks. NIH plans to launch NECTAR in FY 2006.

< *Clinical Research Workforce Training.* Clinical research is a complex endeavor ideally performed by a multidisciplinary team of experts from diverse disciplines who collectively address a common, complex problem. To fulfill the promise of 21st century medicine, innovative multidisciplinary doctoral and pre-doctoral training programs are being implemented in collaborative team settings to support early career development of those with high potential for becoming leaders in various fields of clinical research. On the intramural front, the NIH clinical research-training program for medical and dental students has been doubled. Work is also underway to assess the feasibility of, and to develop optimal model(s) for, establishing a National Clinical Research Associates (NCRA) Program. The NCRA will include a robust infrastructure of trained and qualified community practitioners (e.g., physicians, dentists, and nurse practitioners) who will be positioned to participate in clinical research, to refer and follow patients in clinical studies, and to rapidly transmit research findings to their respective communities. Key elements of the proposed model will be pilot-tested in FY 2006.

< *Regional TranslationalResearch Centers.* Another initiative seeks the establishment of Regional Translational Research Centers (RTRCs). The centers will increase interaction between basic and clinical scientists and accelerate the translational of strategies from the laboratory bench to clinical testing. To do so, the Centers will provide sophisticated advice and resources such as expertise in biostatistics, clinical pharmacology, pharmacogenetics, and genetics. In FY 2004, NIH issued an RFA for RTRC planning grants. Solicitations for formal *Regional Translational Research Centers* are planned for FY 2005 and FY 2006.

< *Clinical Research Policy and Analysis Coordination.* To address the difficulties clinical investigators confront in satisfying the multiple requirements of diverse regulatory and policy agencies, a Clinical Research Policy Analysis and Coordination Program (CRpac) has been implemented to collaborate with other agencies and to help harmonize policies pertaining to clinical research. CRpac foci include developing better processes for, and streamlining of, adverse event reporting, human subjects protection and privacy, conflict-of-interest policies, and standards for electronic data submission.

< *Clinical Outcomes Assessment.* More sensitive and well-validated instruments are needed to assess the fatigue, pain, mood changes, and other subjective symptoms that often accompany debilitating chronic illness. The Patient-Reported Outcomes Measurement Information System (PROMIS) network has been implemented in order to develop and test a large bank of items measuring patient reported outcomes. The initiative aims to create a computerized adaptive testing system that will allow for efficient, psychometrically robust, individualized, and cost effective assessment of patient outcomes across a broad range of chronic diseases. Plans are underway to establish an electronic web-based resource in the public domain for administering computerized adaptive tests and collecting patient reported data. Having a

validated, dynamic system to measure patient-reported outcomes efficiently in participants with a wide range of chronic disorders and demographic characteristics should significantly enhance clinical research and facilitate comparisons across research studies.

< *Public Trust Initiative.* The goal of this Initiative is to improve the public's health by promoting public trust in biomedical and behavioral research. Public Trust Liaisons from every Institute and Center have been selected, and a Public Trust Steering Committee formed. An inventory of Institute and Center activities has been compiled, and a Public Trust website established. An October 2004 workshop held in collaboration with the NIH Director's Council of Public Representatives brought together numerous stakeholder groups, including patients, members of advocacy groups, representatives of community agencies, and researchers to explore next steps for enhancing public trust. The results of the Workshop and inventory will be used to inform and develop specific solicitations and initiatives.

Taken together, the components of the NIH Roadmap represent an ambitious vision for a more efficient and productive system of medical research, with the ultimate goal of improving the length and quality of human life. The collaborative trans-agency process for developing and implementing the NIH Roadmap represents an enhanced approach to portfolio management, and sets a new standard for responding to emerging needs and scientific opportunities.

CHALLENGES AND INITIATIVES

The text below highlights a few of the major areas of research in the NIH research portfolio and examples of scientific initiatives. As NIH monitors shifts in disease burden, development of new health problems, evolving scientific opportunities, and research breakthroughs, the agency determines when targeted initiatives are needed to stimulate research in new directions. These initiatives supplement the body of research projects and programs generated through the free-market of scientific ideas and unanswered questions.

Chronic Diseases

While life expectancy for the U.S. population continues to improve, the burden of chronic disease is increasing. Although progress in prevention and treatment is reducing deaths from heart disease, cancer, and stroke these dreaded diseases remain the three leading causes of mortality in the U.S. At the same time, there is an epidemic of diabetes and obesity putting millions at risk for even more serious diseases. Each of these diseases is complex, and frequently they are interrelated and have common risk factors. For example, heart disease and diabetes are risk factors for stroke. High blood pressure, high cholesterol, and obesity are risk factors for both stroke and heart disease.

Neurological diseases are also a source of premature morbidity and mortality. The burden of Parkinson's disease, Alzheimer's disease, multiple sclerosis, stroke, epilepsy, autism, and many hundreds of other nervous system disorders affects every age group, in every segment of society, among people all over the world. The ever-present and often severe disability associated with these diseases touches both patients and their families. NIH is aggressively seeking to understand and learn new ways to treat and even prevent these complex problems.

Accelerating Research on the Brain: The Neuroscience Blueprint

Several of the most common causes of death and disability, as well as hundreds of rare disorders, affect the brain, spinal cord, or nerve cells in the eye, ear, or elsewhere in the body. The extraordinary range of nervous system disorders encompasses mental illness, neurological disease, drug abuse, alcoholism, chronic pain conditions, developmental disorders, dementias of aging, and myriad problems of hearing, vision and other senses, among many other serious health issues. These disorders affect people of all ages, from the very young, to adults in the prime of life, and the elderly.

Progress in neuroscience has brought recognition of unforeseen interconnections among nervous system disorders, of therapeutic and prevention strategies that may be applicable to many problems, and of how advances in a single area of basic or clinical neuroscience may be relevant to a broad spectrum of disorders. Over the past decade, driven by the science, the NIH neuroscience Institutes and Centers have increasingly joined forces through science-based initiatives and via working groups focused on specific disorders. The NIH Blueprint for Neuroscience Research builds on this foundation, making collaboration a day-to-day part of how the NIH does business in neuroscience. By pooling resources and expertise to address common problems, the Blueprint can increase efficiency and effectiveness, take advantage of economies of scale, and confront challenges too large for any single Institute, while enhancing the mission specific activities of each.

The NIH Institutes and Centers participating in the Blueprint include: the National Institute of Neurological Disorders and Stroke (NINDS), the National Center for Complementary and Alternative Medicine (NCCAM), the National Center for Research Resources (NCRR), the National Eye Institute (NEI), the National Institute on Aging (NIA), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the National Institute of Child Health and Human Development (NICHD), the National Institute on Drug Abuse (NIDA), the National Institute on Deafness and Other Communication Disorders (NIDCD), the National Institute of Dental and Craniofacial Research (NIDCR), the National Institute of Environmental Health Science (NIEHS), the National Institute of General Medical Sciences (NIGMS), the National Institute of Mental Health (NIMH), and the National Institute of Nursing Research (NINR). Each Institute will continue to carry out the basic, disease-specific and life-course specific research unique to its mission. Just at the NIH Roadmap addresses roadblocks that hamper progress across all of medical science, the Blueprint will take on challenges in neuroscience that are best met collectively.

The Blueprint participants are developing initiatives focused on tools, resources, and training. The first activities are designed to have a quick and substantial impact by building on existing programs. These initiatives include a comprehensive inventory and analysis of neuroscience tools funded by the NIH and other government agencies, enhancement of training in the neurobiology of disease for basic neuroscientists, and expansion of Gene Expression Nervous System Atlas, or GENSAT, project beyond the brain to the eye, ear, and other parts of the nervous system. GENSAT is designed to help answer a wide range of questions about how the nervous system develops, works, and what goes wrong in disease by mapping the activity of

thousands of genes. Guided by extensive discussions with representatives of the research community, further Blueprint initiatives include:

- *NeuromouseProject.* More than half of all genes are active in the nervous system. A major challenge in neuroscience, with potential impact on many disorders of the nervous system, is to determine the functions of these genes. One powerful strategy is to investigate the anatomy, physiology, and behavior of mouse models in which specific genes have been deleted. The Neuromouse Project will develop such mouse strains through genetic engineering, focusing on genes that contribute to a healthy or diseased nervous system.

- *Cross-Institute Neuroscience Training Programs.* New inter-institute programs will provide interdisciplinary training in cross-cutting areas such as neuroimaging and computational neurobiology, which have become essential tools to analyze the nervous system in both healthy and diseased states. Related initiatives under development will create training programs that span clinical and basic science departments at universities to encourage physicians and scientists to work together in tackling clinical challenges in neuroscience.

- *Neuroscience Core Grants.* Core facility grants promote interdisciplinary collaboration and cooperation among scientists who use them. The Blueprint will increase efficiency and broaden the impact of core programs by serving laboratories from many NIH Institutes and Centers, rather than a single Institute. Cores are shared across laboratories, and they might include equipment, facilities, and technical support for animal models, cell culture, computer modeling, DNA sequencing, drug screening, gene vectors, imaging, mass spectrometry, microarrays, microscopy, molecular biology, or proteomics among others.

Obesity

One of this century's most daunting chronic health challenges is obesity - a major health problem in its own right and a strong risk factor for type 2 diabetes, heart disease, stroke, certain cancers, osteoarthritis, liver disease, urinary incontinence, sleep apnea, and depression. Over 65 percent of U.S. adults are overweight, with about half of those adults meeting the criteria for obesity. The near tripling of the number of overweight children since 1970 has ominous implications for the development of serious diseases, such as type 2 diabetes, both during youth and later in adulthood. Overweight and obesity also disproportionately affect racial and ethnic minorities and those of lower socioeconomic status.

The obesity epidemic has been fueled by a complex interplay of behavioral, sociocultural, economic, and environmental factors, acting against a backdrop of genetic and other biological factors. Combating the obesity problem requires broad-based national action. The NIH leads the national research efforts through The Strategic Plan for NIH Obesity Research (http://www.obesityresearch.nih.gov/About/strategic-plan.htm). A Task Force established by the NIH Director finalized the plan in 2004 following input from outside experts, interactions with NIH staff at scientific meetings, meetings and workshops convened by NIH institutes and centers, interactions with scientific and health advocacy organizations, and finally solicitations for public comment on a draft plan posted on the internet. The Plan includes short-, intermediate-, and long-term goals for basic, clinical, and population-based obesity research, and

strategies for achieving those goals. Building on scientific advances from previous NIH-supported efforts, the Strategic Plan seeks to maximize collaboration among stakeholders and to capitalize on NIH's collective expertise in developing obesity research initiatives.

The Strategic Plan for NIH Obesity Research outlines how NIH will continue to investigate the molecular and physiologic factors that contribute to obesity, as well as conduct research on obesity-associated diet and physical activity behaviors. For example, NIH investigators identified an elaborate network of hormones and other molecules that connect the brain, gut, fat cells, and other parts of the body to achieve energy balance. One such hormone, ghrelin, stimulates appetite just before meals. Ghrelin is primarily secreted by the stomach, but is also produced in the brain. Increased levels of this appetite-inducing hormone were found in obese individuals following diet-induced weight loss. This finding may explain the difficulty in maintaining weight loss. As hormones like ghrelin are found to contribute to sustaining energy balance, they will become "targets" for drug development. Drugs that home in on these targets could beneficially affect appetite, food absorption, and/or energy expenditure.

Clinical research into obesity prevention and treatment, which includes changes in diet and physical activity, is illuminating both the power of lifestyle interventions and the extraordinary challenges of implementing behavioral approaches. In the Diabetes Prevention Program clinical trial, modest weight loss and exercise conferred a dramatic health benefit - a 58 percent reduced risk of developing type 2 diabetes. This lifestyle intervention surpassed a pharmacologic intervention (the diabetes drug metformin) that was also tested in the trial. Continued behavioral research should greatly enhance the understanding of factors that contribute to obesity and may assist with future design of both pharmacologic and lifestyle interventions. Another active area of research is the evaluation of different types of diets. Scientists found that decreases in the energy density of foods (calories per gram of food) lead to decreased food intake, independent of the fat content. While long-term trials are needed, the results suggest one possible strategy for reducing food intake. Together with studies assessing the effects of different types and amounts of physical activity, these nutritional studies are helping to inform lifestyle-based interventions.

Cardiovascular Disease

Heart disease and stroke-the principal components of cardiovascular (CV) disease-continue to be major causes of morbidity and mortality in the U.S. Heart disease and stroke account for 40 percent of all deaths. Moreover, CV diseases are chronic and cause disability for enormous numbers of Americans. Almost one-fourth of the nation lives with these largely preventable conditions.

While mortality and morbidity from CV diseases are high, we are making progress. Deaths from heart disease and stroke declined substantially over the last 30 years, thanks, in part, to new knowledge gained through NIH research. NIH research played an important role in the identification of risk factors associated with CV disease and the development of a variety of strategies which seek to treat or delay the onset of chronic diseases. These strategies include behavior modification, such as smoking cessation, improved diet, and increased exercise; the increased use of aspirin as both a preventive and treatment for heart disease; improved treatments such as angioplasty and the coronary artery bypass graft; and the development of drugs to control

high blood pressure and cholesterol. Among recent developments is the new cholesterol guideline for persons with high risk of heart attack. Recent clinical trials have shown that people at high risk should push the levels of their low-density lipoprotein (LDL, the "bad cholesterol") even lower than originally thought. To further accelerate progress in the fight against CV diseases, NIH is launching several new initiatives, including:

< *Innovative Targets and Therapy Development for Ischemic Stroke.* NIH is seeking to identify new molecular targets and develop innovative therapeutics for cerebral ischemia (impairment of blood flow to the brain). Ischemic stroke, which usually occurs as a result of blockage in an artery, is a leading cause of death and long-term disability in the U.S. Prompt restoration of blood flow to the brain can limit stroke damage, but the current approach carries a risk of side effects and is useful only during the first few hours after a stroke occurs. New therapeutics that reduce the risk of bleeding, minimize neurological damage, and function over longer time periods are urgently needed.

< *Technologies for Engineering Small Blood Vessels.* A new interagency program involving seven NIH components, the Food and Drug Administration, the National Institute of Standards and Technology, and the National Science Foundation will work together to create living replacement blood vessels that are able to propagate and repair themselves. Such vessels are urgently needed because the supply of adequate native vessels to use as grafts does not meet demand, and current small-diameter prosthetic grafts fail at unacceptable rates. The new initiative will focus on engineered blood vessel substitutes applicable to coronary artery disease, peripheral vascular disease, and congenital heart disease.

< *Heart Failure Clinical Research Network.* Due to the success in reducing the mortality and morbidity of actue coronary hear disease and the lengthening of life expectancy, chronic heart failure in an older population is emerging as a new public health challenge. NIH is establishing a clinical research network to improve outcomes for patients with heart failure. Innovative strategies to repair or restore heart function are emerging and improved mechanical systems are evolving, but will require systematic clinical evaluation. This research network will enable rapid translation of promising research findings into clinical applications, and will facilitate implementation of multiple clinical studies that may demonstrate the promise of new therapies and furnish the necessary background for larger phase III clinical trials.

Cancer

Significant progress has been made since the National Cancer Act was passed over 30 years ago. As reported in the most recent National Cancer Institute Annual Report to the Nation, the risk of getting and dying from cancer in the U.S. continues to decline and survival rates for many cancers continue to improve. Overall incidence rates dropped 0.5 percent per year from 1991 to 2001. Among men, incidence rates declined for leukemia and for cancer of the lung, colon, oral cavity, stomach, pancreas, and larynx. Among women, incidence rates declined for cancer of the lung, colon, cervix, pancreas, ovary, and oral cavity. Significantly, death rates from lung cancer in women leveled off for the first time between 1995 and 2001, after several decades of increase. Comparing five-year survival rates of cancer patients diagnosed in the years 1975 to 1979 to

those diagnosed from 1995 to 2000, analysts found that survival substantially improved for nearly all of the 15 most common cancers in adults and the ten most common cancers in children.

However, cancer continues to be a major challenge to the Nation. It remains the number two killer in the U.S., and U.S. residents have an almost 1 in 2 chance (46%) of developing an invasive cancer during their lifetime.

Although the challenge of cancer remains daunting, progress in basic science is laying the groundwork for a much-needed transformation in cancer care. As scientists better understand the cancer disease process - the molecular causes of cancer, its development, and progression - they will be able to use this information to discover, develop, and deliver agents that specifically target the causes and progression of particular cancers. Such targeted interventions have the potential to dramatically improve the prevention, early detection, diagnosis, and treatment of cancer. Nonetheless, considerable research is still needed. Fiscal Year 2006 initiatives include:

< *Biomarker Discovery.* The discovery and validation of cancer biomarkers will be an integral component of the effort to develop new cancer interventions. Biomarkers have several functions, one of which is to provide early indication of the presence of a disease, such as cancer. Because biomarkers often are substances such as DNA or proteins, the discovery and use of biomarkers will require technologies that can detect these substances with a high degree of specificity and sensitivity, sometimes when they are only present in minute quantities. Also needed is a highly organized approach to the analysis of protein patterns found in the body fluids of cancer patients. Two other important reasons for NIH to pursue this course of research are to capture its potential to inform the discovery and development of drugs and to open new doors for monitoring patients' responses to cancer treatment. To prompt additional research in these areas, in FY 2006, NIH will establish a new Clinical Proteomics and Biomarker Discovery Program and will expand support for the development of advanced technology platforms for overcoming protein detection and other barriers to preparing diagnostic methods for clinical testing.

< *Molecular Imaging andBiosensing.* Another challenge is to develop methods to image the interaction between the immune system and cancer. Methods are needed to clarify the relationship between immune responses to tumors and immune responses to normal cells and tissues. New molecular imaging and biosensing technologies can provide clinicians with important details about patients' tissues *in vivo,* enabling faster, more accurate detection and diagnosis, facilitating more precise image-guided therapies, and making it easier to monitor treatment outcomes.

Infectious Diseases

The NIH is a global leader in research into infectious diseases, which are the second most frequent cause of death worldwide and the third leading cause of death in the United States. Despite remarkable advances in medical research and treatments during the 20th century, infectious diseases remain among the leading causes of death worldwide for the following

reasons: (1) emergence of new infectious diseases; (2) re-emergence of old infectious diseases; and (3) persistence of intractable infectious diseases.

Bioterrorism

The intentional release of anthrax in 2001 underscored the seriousness of the threat of bioterrorism. In addition to anthrax, the microbes of most concern are smallpox, plague, tularemia, haemorrhagic fevers, and botulinum toxin. These "Category A," agents are highly lethal and have the potential to be deployed as bioweapons.

Considerable progress has been made in a short time in finding new means to protect the Nation from the intentional release of infectious agents. The search for vaccines for anthrax and Ebola, and the pursuit of a next-generation vaccine against smallpox led to promising vaccine candidates now undergoing clinical trials. In addition, NIH-supported investigators uncovered the three-dimensional structure of the anthrax toxin complex, giving scientists an additional potential target for blocking the toxin's effects. NIH researchers also developed an animal model (mouse) for use in research on plague.

In FY 2006, NIH will continue to use the Public Health and Social Services Emergency Fund (PHSSEF) to develop nuclear and radiological medical countermeasures which prevent injury and restore damaged tissue. As a companion program, the new chemical countermeasures initiative will support basic research leading to the development of therapies and drugs to help mitigate the effects of exposure to chemical agents. In addition to PHSSEF initiatives, funds appropriated directly to NIH will be used for advanced development of medical countermeasures that will be used against biological threats including those genetically engineered to evade diction of known therapies.

Project BioShield legislation, which was signed into law in July 2004, will help expedite the conduct of NIH research and development on medical countermeasures. Shortly after the signing of the Project BioShield legislation, NIH announced new initiatives to expand biodefense research and product development.

Highlights of planned future research initiatives include:

- *Drug Development Resources for Antiinfectives* and *Cooperative Research Partnerships for Biodefense*

- *Development of a Multivalent Recombinant Botulinum Vaccine*

Emerging and Re-Emerging Diseases

Unfortunately, the viruses, bacteria, and parasites that cause infectious diseases do not remain static, but continually and dramatically change over time as new pathogens emerge and as familiar ones re-emerge with new properties or in unfamiliar settings. For example, since AIDS was first recognized in 1981, this emerging disease has spread relentlessly throughout the world. In the past five years alone, West Nile and monkeypox viruses emerged in the United States,

while Asia experienced an unprecedented number of human infections with avian influenza viruses and the emergence of a new infectious disease, SARS.

Influenza, West Nile virus, Lyme disease, malaria, tuberculosis, *Staphylococcus aureus, Streptococcus pneumoniae,* cholera, diphtheria, and plague all recently increased in incidence or geographic range and/or became evident in a new human group. These microbes acclimated to new ecological niches, reached and adapted to new hosts, and/or became antibiotic resistant.

The emergence or re-emergence can be frightening, but as basic knowledge and sophisticated research tools accumulate, we are responding to these challenges more rapidly. For example, within weeks of the first SARS reports, NIH-funded researchers and their colleagues at the Centers for Disease Control and Prevention identified the coronavirus that causes SARS and developed diagnostic tests. Within a year and a half, three new NIH-developed candidate vaccines successfully protected animal models of SARS, and one of these vaccines is now in human clinical trials.

Ongoing NIH-funded efforts promise to yield new tools in the fight against emerging and re-emerging infectious diseases. For example, NIH-supported investigators are evaluating an innovative treatment for encephalitis (an inflammation of the brain) due to West Nile Virus infection. In addition, accelerated efforts to develop malaria vaccines reached a milestone with the first launch of a clinical trial in Mali, a country where malaria is endemic. The trial reflects many years of collaboration between NIH, the Walter Reed Army Institute of Research, GlaxoSmithKline Biologicals, the U.S. Agency for International Development, the World Health Organization, and the Malian Ministries of Health and Education.

The inadequacy of the current vaccine against tuberculosis (TB), coupled with the ability of the tuberculosis bacterium to develop resistance to anti-TB drugs, makes it urgent that we develop new TB vaccines. Advances in understanding the bacterium that causes TB led to the first new vaccine to be tested in the U.S. in 60 years. In addition, avian influenza appeared in humans more frequently, with outbreaks of new strains of the virus. The fact that these viruses continually mutate raises fears of a more communicable strain, one that would cause a global pandemic. In fact, NIH-funded researchers recently discovered that avian influenza has become endemic in waterfowl in east Asia. NIH is vigorously supporting research to develop vaccines against these newly emerging viral strains.

In recent progress against HIV/AIDS, scientists showed that a simpler regimen of anti-HIV drugs may be used by some patients to reduce the cost and toxicity of HIV/AIDS treatment. Researchers also found a viral protein that is essential for viral replication also blocks anti-HIV activity of a host protein.

To address the challenge of emerging and re-emerging diseases, NIH is pursuing planned future initiatives, such as the following:

- *HIV/AIDS Clinical Trials Network.* A major restructuring of the HIV/AIDS clinical research program is designed to increase efficiency and improve the integration of prevention, vaccine and therapeutic research. This initiative responds to the global research needs posed by the

AIDS pandemic, particularly in resource-limited settings, and focuses research efforts on six areas of highest scientific priority.

- *Pandemic Preparedness in Asia:* Expansion of a contract for surveillance and characterization of avian influenza viruses.

- *Drug Development Resources for Antiinfectives.* This initiative will accelerate development of antimicrobials by providing a flexible menu of resources for preclinical drug development to the scientific community and industry partners.

Non-Biodefense Partnerships: Vaccines for Hepatitis C. This initiative will stimulate industry participation in the development of vaccines for hepatitis C.

Health Disparities

Despite tremendous medical advances and improved public health in recent decades, African Americans, Hispanic/Latino Americans, American Indians, Alaska Natives, Asians, Native Hawaiians, and Other Pacific Islanders, and medically underserved communities continue to suffer an unequal burden of illness, premature death, and disability in the U.S. The risk for diabetes is a case in point. Compared to adult non-Hispanic whites of similar age, the likelihood of having diabetes is 1.5 times higher for Hispanic/Latino Americans, 1.6 times higher for non-Hispanic blacks, and 2.3 times higher for American Indians and Alaska Natives. Recognizing the urgency of the type 2 diabetes epidemic, and the differential risk for minority groups, NIH and the Centers for Disease Control and Prevention have collaborated to develop and launch *"Small Steps. Big Rewards. Prevent Type 2 Diabetes,"* a national multicultural diabetes prevention campaign.

Cancer incidence and death rates also reveal significant differences by race/ethnicity and socioeconomic status. From all cancers combined, the highest incidence and death is for African Americans. Five-year survival rates are lower for men of American Indian/Alaskan Native and Asian American/Pacific Island descent and for women of African American and American Indian/Alaskan Native descent.

Under the umbrella of the NIH Strategic Plan to Reduce Health Disparities, there is ongoing research into the biological, social, and environmental basis for health disparities; activities to foster cancer awareness among all populations; and efforts to increase the number of minority scientists in biomedical research. For example, NIH is an active participant in the DHHS Stroke Belt Elimination.

Building on the base of ongoing research on health disparities, NIH plans to launch new and expanded initiatives.

< *Training in Community-Based Participatory Research.* The NIH plans to develop pre- and postdoctoral training grants in community-based participatory research. Funding will be provided for research studies looking at the interface of physical and psychosocial

environments and their health impacts on communities of color and the medically underserved.

< *The Risk of Cardiovascular and Lung Diseases in Hispanic Populations.* The NIH will support a multicenter epidemiologic study to improve knowledge of the burden of cardiovascular and lung diseases among various U.S. Hispanic groups, determine the role of acculturation in the prevalence and development of the diseases, and identify factors that confer susceptibility or risk.

< *Trans-NIH Working Group and Clinical Research Network on Sickle Cell Disease.* Sickle cell disease (SCD) continues to be a significant cause of mortality, morbidity, and health disparities in the US and globally. In November 2003, NIH held a conference entitled "New Directions for Sickle Cell Therapy in the Genome Era," in November 2003. Over 120 individuals from the US and abroad took part in the conference. A trans-NIH staff working group, co-chaired by NHGRI and NHLBI, was formed, including representation from eight institutes and centers, to follow up on the recommendations from the conference. In addition, a Sickle Cell Disease Clinical Research Network is planned to address critical issues in the care of patients with sickle cell disease.

< *The Community Networks Program (CNP) to Reduce Cancer Health Disparities.* The NIH will support grants to reduce cancer health disparities in racial/ethnic minorities and underserved communities throughout the U.S. using community-based participatory cancer education, research, and training in 2005. The goal of the CNP is to significantly improve access to, and utilization of, beneficial cancer interventions in communities with cancer health disparities and to reduce those disparities or inequalities."

SCIENCE ADVANCES

The following section provides additional examples of recent achievements, to supplement the scientific advances described along with the challenges and initiatives above. The scientific advances reported herein are the outcome of many and varied investments in medical research by the NIH, some of which began more than a decade ago.

Progress in Neuroscience

The Link between Ritalin and Dopamine. Considerable progress is being made in unraveling the neurologic basis for behavioral disorders, including Attention Deficit Hyperactivity Disorder (ADHD). The most commonly diagnosed behavioral disorder in childhood, ADHD is routinely treated with methylphenidate (Ritalin); however, Ritalin's mechanism of action was not understood. A recent study showed that healthy volunteers, who received Ritalin before working through mathematical tasks, displayed a significant increase in the brain chemical dopamine and were more likely to describe their assignment as exciting and motivating. Since dopamine mediates motivational responses, Ritalin may act by enhancing the interest value of complex tasks. This link between Ritalin and dopamine explains how Ritalin may help people with ADHD improve their focus and motivation for performing academic tasks. Further knowledge

of the mechanism of Ritalin action may contribute to improved understanding of ADHD and inform future treatment and drug development.

Basic Research on Alcoholism. Substances of abuse, including cocaine, heroin, and alcohol, all target what is called the brain's "reward circuit" - specific areas of the brain that are involved in the pursuit of rewards and the gratification in achieving them. Alcoholism is ranked third in the Centers for Disease Control and Prevention's list of preventable causes of death. In a search for better molecular targets for medication development, scientists zeroed in on the site where alcohol molecules bind to cell membranes. Alcohol is known to affect many of the neurotransmitter receptors present in cell membranes, and now scientists are visualizing the pocket that alcohol slips into in an alcohol-sensing protein. This long-sought discovery raises the possibility of disrupting the binding pocket in key receptors to prevent alcohol from affecting brain cells.

Combating Neurodegenerative Diseases. Inroads likewise are being made in devising strategies to combat neurodegenerative diseases. Patients suffering from a host of neurodegenerative conditions, such as Parkinson's disease, prion (Creutzfeld-Jacob) disease, Huntington's disease, Lou Gehrig's disease, and Alzheimer's disease, typically have abnormal clumps of macromolecules scattered throughout their brains. Scientists are exploring ways to prevent the formation of these clumps of molecules. Up to 4 million Americans are affected by Alzheimer's disease, in which accumulating P-amyloid proteins clog the brain. By attaching small inhibitors to the proteins that fold amyloid into the proper shape, researchers prevented amyloid proteins from latching onto each other to form clumps. This approach may provide an innovative way to block the macromolecular clumping that characterizes many neurodegenerative diseases.

Potential Treatment for Chronic Pain. Frequently the best available treatment for the 34 million adults afflicted by moderate to severe chronic pain is opioid-based analgesics, such as morphine, oxycodone and dilaudid, which are addictive and do not provide relief for all types of pain. Other interventional therapies, including implantable devices, are nonselective (i.e., in addition to deadening pain, they kill-off nerves important for feeling and movement), expensive, potentially ineffective, or accompanied by serious side effects. These shortcomings highlight the tremendous need for novel, effective approaches to pain management. Recently intramural NIH scientists established the therapeutic potential of selectively eliminating those nerve cells that convey severe chronic pain. Some pain-transmitting cells are coated with a protein that can be targeted by a 2000 year old drug from a North African succulent plant (resiniferatoxin, or RTX). RTX ultimately kills these nerve cells while leaving unscathed neighboring nerve cells that are responsible for other body sensations or muscle control. An initial series of experiments in rats showed that a single injection of RTX in areas that supply sensation to the face or body eliminated pain-transmitting cells. The treatment was next tested and found successful on dogs that were admitted to veterinary hospitals with severe pain from arthritis or cancer and were candidates for euthanasia. The treatment was highly effective in all the dogs. The next goal is to move the treatment into early stage clinical trials for people with severe, cancer pain that is unresponsive to conventional medications and therapies.

Advances in Genetics and Genomics Research

With completion of the sequencing of the human genome in April 2003, scientists are focusing on identifying the function of genes involved in health and disease, characterizing genetic variation, and translating these discoveries into diagnostics, prevention strategies, and treatments.

Linking Genes to Diseases

During FY 2004, NIH-funded researchers identified numerous genes implicated in disease. For example, a research team composed of scientists from NIH and around the world identified variants in a gene that may predispose people to type 2 diabetes, which affects roughly 17 million people nationwide. This form of diabetes, which disproportionately affects African Americans, Hispanic/Latino Americans, and American Indians, is characterized by a failure of the pancreas to produce enough insulin. The researchers identified four genetic variants that are strongly associated with type 2 diabetes in two different populations. These variants are all located in the regulatory region of a gene that influences the production of insulin, and they increase a person's risk of developing type 2 diabetes by 20 to 30 percent. The tools of genomics are beginning to reveal many details about the risk of diabetes and other common diseases that had previously been unapproachable.

Scientists also recently identified a gene variant linked to alcohol tolerance in the worm *C. elegans*. Alcoholism is rooted in the brain, where a variety of proteins mediate alcohol's actions in nerve cells; variation in the genes that encode these proteins can affect a person's risk for alcoholism. NIH-funded researchers compared two groups of worms with different responses to alcohol, and found that a variant of a gene encoding a brain protein (called NPR-1) was associated with the ability to drink more alcohol, which raises the risk of alcoholism. The equivalent gene in humans (called NPY) has been intensely studied by alcohol researchers, who have shown that it can influence how much alcohol people drink. These findings raise the possibility that the NPY gene could be a pharmaceutical target or serve as a marker of disease risk.

Tools for Analyzing Genome Sequences

Genetic discoveries will drive the development of diagnostics to identify people at risk for heritable disorders, support the creation of animal disease models for detailed study of pathogenic mechanisms, and guide the search for potential therapeutic mechanisms. But the process of individually identifying the gene variants that play a role in most common diseases (such as diabetes, heart disease, and mental illness) is slow and arduous. The task is complicated for the common diseases, because typically a single gene doesn't determine whether an individual has diabetes or heart disease. Instead, the actions of many genes, each of which may contribute only a small part, figure in the disease process. What researchers urgently need is a way to scan through the genome to quickly find the genetic variants that predispose individuals to common complex diseases.

To facilitate this process, NIH is spearheading an ambitious effort to create the next-generation map of the human genome—the "HapMap," a catalog of how genetic variations are correlated in DNA neighborhoods (called "haplotypes"). The HapMap will provide significant savings in time, effort, and cost in uncovering hereditary factors in disease. To create the HapMap, researchers have sampled 270 people from selected populations around the globe, and have already identified 9 million genetic variants that will be used to create the map of DNA

neighborhoods. When completed, the HapMap will serve as a powerful tool that researchers can use to find the gene variants that affect health and disease. The HapMap will also help elucidate the genetic factors contributing to variation in individual response to disease, drugs, and vaccines. This knowledge will enable doctors to genetically screen patients to determine who is at risk for certain diseases and who would most benefit from specific treatments.

For the scientific community to make the best use of the tremendous resource provided by the Human Genome Project, they must determine the identities and locations of the genetic elements that regulate gene expression, control DNA replication, and govern chromosome structure. There is strong evidence that poorly understood parts of the human genome contain such "functional elements," but little information exists about where these functional elements are located—or how they work. To address this challenge, NIH launched the Encyclopedia of DNA Elements (ENCODE) project with the goal of identifying the precise location and function of all functional genetic elements in the genome. This knowledge will enable us to mine and fully utilize the human genome sequence. All the data generated from the project will be deposited in free, public databases. In the fall of 2004, NIH announced a new set of technology development grants designed to ensure that scientists have the toolbox necessary to identify and characterize genetic functional elements.

The availability of the complete human genome sequence—as well as those for other organisms—is driving the development of an exciting new field of biological research called comparative genetics. By comparing the human genome sequence with the genomes of other animals, scientists can better understand the structure and function of human genes in order to develop new strategies to combat human disease. In support of this approach to understanding the genome, NIH is funding the next generation of large-scale sequencing centers. NIH-funded sequencing teams have also recently assembled the draft sequences of rat, cow, dog, and several other important genomes.

Translating Genomic Advances into Therapies

Ultimately, we hope to translate the discovery of genes associated with disease into new therapies, and NIH is committed to the development of new technologies to correct genetic defects. The use of gene therapy to replace defective genes is one technique that has shown much progress. However, a major challenge in gene therapy is controlling the expression of a transplanted gene once it has been delivered into a cell. Recently, NIH researchers found a new version of a gene-carrying vehicle (known as a vector) that exhibits excellent long-term performance. The vector was built from a common virus and carried the gene for erythropoietin, a hormone that stimulates the production of red blood cells. Two years ago, the NIH team showed that this bioengineered vector worked well when injected in mice. Left unanswered, however, was whether the gene vector could keep up the good work over a longer period of time. In the new study, the researchers showed that the transplanted erythropoietin gene succeeded in stimulating red blood cell production for over a year. Importantly, they detected no signs of an adverse immune response, a common setback in gene therapy experiments. These results clear the way for work in larger animals, which would allow the scientists to better scale the likely therapeutic dosage for humans for possible clinical trials.

In another gene therapy advance, researchers supported by NIH have reported a significant improvement in an approach to treating muscular dystrophy (MD) in mice. Previous work showed that MD could be prevented in a mouse model of the disease by replacing a defected gene (called dystrophin) with a corrected copy. However, until now, no one had found a method in which a new gene could be delivered to all muscles of an adult animal, including those that had already developed MD. The researchers injected the normal dystrophin gene into a viral vector together with a protein (vascular endothelium growth factor) that allows the vector to move through the blood vessel walls into the muscles. This method of gene therapy succeeded in reaching all damaged muscles in a mouse and significantly improved muscle function. The results bolster current efforts to better understand and treat MD, a group of diseases for which there is not yet any effective treatment. The same approach may be used to treat other muscle diseases.

NIH is also pursuing the development of new tools to turn off or "silence" specific genes. NIH-funded research has resulted in the development one such technique, called RNA interference (RNAi). RNAi can be used to elucidate the function of specific genes and identify new drug targets, and even to silence harmful genes. Indeed, recent NIH-funded work demonstrates that RNAi can be a powerful tool to treat disease. The research team, which included NIH and NIH-funded scientists, used RNAi to suppress the activity of a gene in mice that causes a neurodegenerative disorder. The treated mice showed improved movement control and a healthier brain structure than untreated mice. RNA interference may be useful for treating many disorders; other research teams have recently found promising results applying the technique to inactivate a harmful gene in an animal model of Lou Gehrig's disease (amyotrphic lateral sclerosis, or ALS) and to silence genes responsible for proliferation of tumor cells in an animal model of brain tumors.

NIH has always been at the vanguard of genomic research, and will continue to lead the way toward the ultimate goal of using genetic information to diagnose, treat, and prevent disease.

Harnessing the Immune System

The immune system is a collection of cells and proteins that works to protect the body from potentially harmful, infectious microorganisms such as bacteria, viruses, and fungi. The immune system is also responsible for allergies, autoimmune diseases, and the rejection of transplanted organs, cells, tissues, and medical implants.

The past two decades of intensive and highly productive research on immune mechanisms have resulted in a wealth of new discoveries, which promise to lead to major advances in the diagnosis, prevention, and treatment of a broad range of human diseases involving the immune system. Importantly, these new treatments may someday replace powerful immune-suppressing drugs that must be given to patients to prevent rejection of organ transplants but leave these patients vulnerable to a host of infectious agents and other serious side effects.

Developing Immune Tolerance

One of the most exciting areas of research in immunologic diseases involves selectively blocking inappropriate immune responses while leaving protective immune responses intact. This strategy is called induction of immune tolerance.

NIH-supported scientists discovered a promising method for developing immune tolerance to heart transplants by exploiting the immune system's natural mechanism for distinguishing "self from "nonself" tissues. Transplant rejection occurs when the immune system attacks a transplanted organ that is recognized as "nonself." Normally, "self tissues are protected by a process in the developing thymus where immune cells capable of attacking "self" tissues are destroyed. To eliminate immune cells that would attack the "nonself" donor organ, and allow the recipient's immune system to "tolerate" the transplanted organ, researchers transplanted a lobe of thymus from the organ donor along with the donor's heart in a pig transplant model. The organ recipients that received a lobe of thymus lived longer and experienced less organ rejection than pigs that received only the transplanted heart. In humans, the thymus becomes inactive by adulthood, but this experimental procedure could potentially be applicable for children. This innovative new method may prevent organ rejection, reduce the need for immunosuppressive drugs, and greatly improve the quality of life of children who receive transplants.

As basic immune mechanisms continue to be more fully understood, the thorough evaluation of novel, tolerance-inducing therapies is essential. NIH, in conjunction with the Juvenile Diabetes Research Foundation supports the *Immune Tolerance Network*. The Network is a collaborative research effort that solicits, develops, implements, and assesses clinical strategies and biological assays for the purposes of inducing, maintaining, and monitoring tolerance in humans for transplantation, autoimmune diseases, allergy, and asthma.

Addressing Autoimmunity

Autoimmune diseases result from a dysfunction of the immune system in which the body attacks its own organs, tissues, and cells as foreign. The body has safeguards to prevent the immune system from attacking its own tissues, but when these safeguards are breached, an autoimmune disease can result. Medical science has identified more than 80 clinically distinct autoimmune diseases. The social and financial burdens imposed by these chronic, debilitating diseases include substantial loss of productivity and high health care costs.

For the millions of Americans with rheumatoid arthritis-an autoimmune disease in which the immune system attacks and damages joint tissues-increased basic understanding of the workings of the immune system led to a treatment strategy to selectively suppress the abnormal immune response that causes the disease, while leaving the body's ability to fight bacteria and viruses intact. Researchers found that rheumatoid arthritis patients have an abnormal, over-zealous response to a normal protein produced on the surface of cells during an immune response. By giving patients a synthetic version of the protein, scientists were able to train the immune system to tolerate the normal protein, rather than see it as foreign and attack it. This innovative approach is now being tested in a larger study to determine whether the changes in the response of the "trained" immune system actually result in decreased symptoms in rheumatoid arthritis patients.

The NIH continues to support a broad range of basic and clinical research programs in autoimmunity, including several multicenter research programs such as the *Autoimmunity Centers of Excellence* that conduct collaborative basic and clinical research on autoimmune diseases. The most common of these diseases include systemic lupus erythematosus, multiple sclerosis, type 1 diabetes mellitus, and rheumatoid arthritis. Additional programs such as the *Autoimmune Diseases Prevention Centers* will focus on prevention of autoimmune disease before clinical onset.

Treating Allergic Diseases

Allergic diseases and asthma are major causes of illness and disability in the U.S.; more than 50 million Americans suffer from allergies, asthma, or both, and the cost to the health care system is more than $14 billion annually. An allergy is a specific reaction of the body's immune system to a normally harmless substance. NIH supported scientists discovered that people with chronic sinusitis, many of whom also suffer from allergies and asthma, have an exaggerated immune response to common airborne fungi. After determining that the levels of fungal proteins in nasal secretions were similar in both normal volunteers and sinusitis sufferers (indicating that the mere presence of fungi in the airways is not enough to cause sinusitis), the investigators looked for evidence that immune cells from people with sinusitis respond abnormally to harmless fungi. The studies revealed that, compared to the cells of normal individuals, the immune cells of chronic sinusitis sufferers released significantly greater amounts of three immune-modulating chemicals, called cytokines. This study is the first to show a possible immunologic basis for chronic sinusitis, which affects nearly 30 million Americans and costs over $5.6 billion per year. Importantly, the results suggest a potential treatment for these patients using readily available anti-fungal drugs.

In order to continue to make these types of seminal discoveries, which offer potential new therapies for allergic diseases, future initiatives include continued support of the *Asthma and Allergic Diseases Research Centers,* which conduct basic and clinical research on the mechanisms, diagnosis, treatment, and prevention of asthma and allergic diseases. In addition, the *Food Allergy Research Consortium* is a new effort to provide critical information on the pathophysiology and natural history of food allergies and develop effective preventive interventions.

Progress Against Infectious Disease

Co-infection with Harmless Virus Increases Survival of HIV-Infected Men. Scientists found that men infected with both HIV and an apparently harmless virus called GBV-C were three times *less* likely to die than HIV-positive men not infected with GBV-C. Subsequent studies indicated that GBV-C inhibits HIV by increasing the levels of certain factors that suppress the growth of the deadly virus. Further study of the mechanism through which GBV-C prolongs the survival of individuals infected with HIV-1 may lead to the identification of targets for the development of novel therapies to combat HIV/AIDS. In addition, this research provides clues as to why the course of HIV-1 infection is so variable among individuals.

Cutting Edge Technology Blocks Flu Infection. An innovative strategy developed by a team of NIH-funded scientists may lead to the development of novel ways to treat, and perhaps prevent, influenza infection. The scientists designed short interfering RNA (siRNA) molecules that

targeted and inactivated two influenza proteins essential for infection. These siRNAs, when given to mice before or after viral infection, blocked virus production in the lungs and effectively prevented and treated influenza infection. Although these siRNAs have yet to be tested in humans, these exciting findings suggest that one day this powerful new technology may be used to effectively prevent or treat influenza infections in people.

First U.S. SARS Vaccine Trial Opens. Harnessing modern molecular genetics, NIH scientists developed three distinct SARS vaccine candidates over the past year, all of which offered protection in animals. Now, the first of those candidates is being tested in a clinical trial in 10 healthy volunteers at the NIH Vaccine Research Center. This trial was launched just 21 months after SARS was recognized as a new infectious disease. The study will determine if the experimental vaccine is safe in people and assess how well the vaccine stimulates the immune system's response against the SARS virus. The vaccine was developed at an unprecedented pace through the use of new technological innovations.

Progress Against Health Disparities

A Simple Intervention Significantly Delays and Prevents Glaucoma in African Americans. Elevated pressure inside the eye is thought to be the leading risk factor for the development of glaucoma; but, until the initial findings of Ocular Hypertension Treatment Study (OHTS) were released, there was no definitive demonstration that reduction of such pressure prevents or delays glaucoma. In 2002, the OHTS showed that, after five years of treatment, eye drops to reduce pressure inside the eye reduced the onset of glaucoma by more than 50 percent. Because glaucoma is a leading cause of blindness and visual impairment among African Americans, researchers wanted a more definitive answer about the effects of early treatment in this population. The researchers continued to follow African American study participants and found that pressure-lowering eye drops were almost as successful. With knowledge of a simple intervention now in hand, it is even more important to identify African Americans at risk for development of glaucoma, so that they can receive prompt evaluation for possible medical treatment.

Latinos Have High Rates of Blindness and Visual Impairment. Results from the Los Angeles Latino Eye Study (LALES) indicate that Latinos have some of the highest rates of visual impairment and blindness in the United States. Socio-economic factors such as unemployment, divorce, and low education levels were associated with increased rates of visual impairment and blindness. Almost a quarter of the LALES population had diabetes, a rate that is twice that of Caucasians, and half those diagnosed with diabetes had signs of diabetic retinopathy. About 20 percent of individuals with diabetes were not aware of their disease until they were diagnosed during their LALES exam. The prevalence of glaucoma was also high (4.3 percent) and increased dramatically with age. Of the Latinos with glaucoma and ocular hypertension, 75 percent were undiagnosed before the study. About 10 percent had early signs of age-related macular degeneration. One in five adult Latinos had a cataract. These statistics will aide public health professionals in devising strategies to target at-risk populations for screening and treatment.

Hormone Replacement Therapy: The Foundation for Evidence-Based Choices. As recently as three years ago, a substantial number of postmenopausal American women were taking some form of hormone replacement therapy (HRT) in the expectation that it would not only reduce menopausal symptoms but also reduce their risk of developing certain chronic diseases. Now, the results of the second Women's Health Initiative (WHI) clinical trial, a trial on estrogen alone, have provided the findings needed for evidenced-based decision-making about the risks and benefits of HRT. The findings are clear: HRT - whether estrogen plus progestin or estrogen alone - should not be used to prevent chronic disease, but rather, only to treat menopausal symptoms, and with the lowest dose and for the shortest time possible.

Other Science Advances

Immune Responses to Carbohydrates May Underlie Several Common Diseases. Research on basic carbohydrate chemistry unexpectedly revealed that some foods appear to cause an immune response and, therefore, may contribute to the progression of diseases with immune-mediated and inflammatory components. NIH-funded scientists studied a carbohydrate molecule that humans do not make, but that is present in high levels in red meat and milk. Surprisingly, the carbohydrate is able to infiltrate directly into the cells of human tissues and provoke an immune response that may cause long-term inflammatory reactions in body tissues. Such an immune response could contribute to inflammation involved in heart disease and increase the risk for some autoimmune diseases like rheumatoid arthritis.

The Unified Medical Language System (UMLS) Incorporates SNOMED CT. The Federal government is calling for current, readily available, electronic health records for most Americans within a decade. The plan to computerize health care information would both improve the quality of health care and yield cost savings. However, without a common electronic medical terminology standard, it is nearly impossible to integrate data from various patient information systems to create a complete, current medical record. In 1986, NIH began development of the Unified Medical Language System (UMLS), a large-scale biomedical terminology project to facilitate information sharing, dissemination, and retrieval by bringing together many existing biomedical terminologies. The UMLS is available free of charge to licensed users. Now, UMLS also incorporates SNOMED CT (Systematized Nomenclature of Medicine - Clinical Terms) the world's most comprehensive database of clinical terminology.

New Means for Imaging at the Molecular Level. Molecular probes are small molecules that allow visualization or imaging of biological processes in cells and tissues. Also known as molecular beacons, these probes offer researchers a new tool to gather information about the fundamental actions and reactions that occur at molecular levels. One form of molecular probe that is generating interest is semiconductor nanocrystals. These microscopic particles exhibit unique optical properties that allow scientists to obtain clear images from deep within body tissues with little background "noise." However, some nanocrystals are toxic and unstable. A group of scientists developed a special coating to reduce nanocrystal toxicity and improve stability while maintaining their unique optical properties. The development and improvement of these nanocrystals will now enable scientists to safely obtain clear images of cellular activity from deep within body tissues and significantly enhance the study of a number of important disease processes at the molecular level.

Discovery of Biological Basis for Obesity-Associated Hypertension Provides Clue to Preventives. For years scientists have known that obese individuals are prone to develop hypertension (high blood pressure), which, in turn, increases risk for heart disease and stroke. This association is especially true among people with excess abdominal fat. The development of drugs to prevent obesity-associated hypertension, however, has been hindered by a lack of understanding of the biological basis for the problem. In studies with rats, investigators recently showed that a protein produced by abdominal fat cells, angiotensinogen, contributes to obesity-related hypertension. If a similar process is found to contribute to obesity-related hypertension in humans, angiotensinogen production by abdominal fat cells could prove to be a valuable new target for therapies to prevent obesity-related hypertension.

Extended Outpatient Rehabilitation Improves Independence after Hip Fracture. Hip fractures are common in the elderly and can have a devastating impact on ability to remain independent. Despite standard rehabilitation, up to three-fourths of patients with hip fractures fail to regain their walking ability or functional status within twelve months. Now, a clinical trial has determined that six months of supervised physical therapy with whole-body, progressive-resistance exercise training produces considerably better outcomes than standard care, which focuses primarily on flexibility. Patients in the intervention group had significantly greater improvements in muscle strength, walking speed, and balance than patients in the control group. These improved outcomes make a noticeable difference in functional status and ability to perform activities of daily living such as eating, bathing, and dressing.

STORY OF DISCOVERY

In the preceding pages, we have described but a few examples of the many scientific advances achieved by NIH-funded researchers. Some represent years of research in the laboratory and the clinic, culminating in a new treatment or prevention strategy. Others reflect the development of innovative technologies or significant new knowledge about fundamental processes in the cell or in the organs and systems that play a role in health or disease—knowledge necessary to the development of clinical applications. We include here a "story of discovery" that we hope explains the multiple and varied paths from the bench to the bedside.

Transdermal patches—medicated adhesive pads placed on the skin that release drugs gradually for up to a week—have been available in the U.S. for more than 20 years. The first transdermal patch, approved by the U.S. Food and Drug Administration in 1979, delivered scopolamine to treat motion sickness. Since then, more than 35 transdermal patch products have been approved. Examples include the nicotine patch that helps people quit smoking, the lidocaine patch for relieving pain, and a patch containing sex hormone derivatives for preventing pregnancy.

Transdermal patches have several advantages compared with other methods of drug delivery: they are painless, the drugs are not degraded in the gastrointestinal tract, and they provide a constant dosage without the need for patients to remember to take their medications. In addition, delivering drugs by way of patches can reduce the side effects of some drugs. For example, estrogen patches, unlike estrogen pills, do not cause adverse effects on the liver when used to treat menopausal symptoms.

However, due to permeability constraints of the outer skin layer, the number of drugs that can be administered via transdermal patches is limited. To expand the number of compounds that can be delivered via the skin, researchers are developing novel transdermal technologies.

< **Microneedle Arrays Expand Transdermal Applications**

One promising area of novel transdermal technology is microneedle arrays. The microneedles, with diameters smaller than a strand of hair, create holes in the outer skin layer, thereby allowing passage of large molecules and other compounds that ordinarily could not traverse the skin. The microneedles are painless because they are too small to touch the nerves located deeper in the skin.

Although microneedles were first proposed in the 1970s, the technology needed to make microneedles did not become widely available until the 1990s. Using techniques developed in the microelectronics industry, NIH-supported researchers devised methods for inexpensively mass-producing microneedles from materials such as silicon, metal, and glass. The researchers also showed that microneedles can be made from polymers that will harmlessly degrade in the body, thereby preventing problems should a microneedle break off in the skin. The investigators further demonstrated that microneedles can be constructed to be solid or hollow, and both types can be made with different geometries to allow the administration of different-sized compounds, including drugs, proteins, and vaccines.

One drug-delivery technique uses solid microneedles to create micropores in the skin, and then the drug is applied over this area. NIH-funded scientists recently used this technique to administer insulin to diabetic rats. An array of solid metal microneedles was pressed into the skin, and then a glass chamber filled with insulin solution was placed over the microneedle array. Over a 4-hour time period, blood glucose levels steadily dropped by as much as 80 percent. Another drug-delivery method involves coating solid microneedles with a drug, which is then released from the needles when they are embedded in the skin.

Still another method employs hollow microneedles, which allow drug solutions to be infused through the needles using a microprocessor-controlled pump. NIH-supported scientists recently inserted hollow glass microneedles into the skin of diabetic rats to deliver insulin for 30 minutes. Over a 5-hour period after the insulin was administered, blood glucose levels dropped by as much as 70 percent. Because people would require minimal training to apply microneedles, these devices may prove useful for immunization programs

in developing countries or for mass vaccination or antidote administration in bioterrorism incidents.

< **Increasing Skin Permeability With Low-Frequency Ultrasound**

Another transdermal technology being developed is low-frequency sonophoresis (LFS), which uses low-frequency ultrasound to create pores in the skin that stay open for several hours. In studies with animals, LFS has delivered insulin to diabetic rabbits and the anticoagulant heparin to rats. Recently, scientists used LFS to administer local anesthetics through the skin to human volunteers. To improve the design of LFS systems, NIH-funded researchers have been studying the mechanisms by which LFS increases skin permeability. Scientists found that an ultrasound frequency of 20 kilohertz induces the formation of low-pressure air bubbles on the skin surface.

Researchers have also experimented with viscous substances known as porous resins to increase skin permeability during sonophoresis. When dissolved in a solution of water and alcohol, these resins release air bubbles that trigger the formation of larger bubbles when LFS is applied.

< **Transporting Drugs Using Electroporation**

Still another transdermal technology under development is electroporation, the application of short, high-voltage electrical pulses to create temporary micropores in the skin. Electroporation has been used to transport several drugs through the skin, including insulin, heparin, and the local anesthetic lidocaine. Studies also suggest that electroporation could be used to deliver compounds that would ameliorate skin aging, such as particular genes or Vitamin C. NIH-supported scientists have found that transdermal drug delivery via electroporation can be enhanced through the use of mild heat, alkaline solutions, and sodium dodecyl sulfate (a detergent used in various household products, including toothpaste, shampoo, and cosmetics).

In transdermal drug delivery, because the drug reservoir remains outside the body, these novel devices provide the opportunity to easily adjust the quantity and delivery rate of medications. Future transdermal systems might be controlled by miniature computers, which would allow for accurate dosing as needed by the patient. These systems might also include sensors that monitor blood levels of compounds, such as glucose in diabetics, and then adjust the release of a drug, such as insulin. These and other developments in transdermal drug delivery technologies hold promise for improving patient compliance by making drug administration effortless as well as and painless.

MANAGEMENT INNOVATIONS

The NIH took action to implement a variety of innovations in management and plans to continue to building upon its successes. These innovations have been recognized within the Department as well as by outside organizations, and a few examples are highlighted below.

Improved Grants Management Operations and Oversight. The NIH Extramural Research Program received the highest possible rating of "Effective" in the FY 2006 Program Assessment Rating Tool (PART) review by the Office of Management and Budget. Specific information about the results of the PART review is provided earlier in this document. Also, as part of the President's Management Agenda (PMA), the NIH continued its progress in the e-government arena, with the further development and extension of its electronic Grants Administration system (eRA). In July 2004, the eRA initiative was recognized as a center of excellence by HHS with a Secretary's Award for Distinguished Service. NIH continues to ensure that the eRA systems are collaborative endeavors of the full NIH community and its partners that are establishing a system for end-to-end electronic processing of research grants. The Centers for Disease Control and Prevention (CDC) migrated to this system exclusively for research grants, and NIH is working with the Food and Drug Administration for their transition in 2005. In FY 2004, NIH fully implemented the new OMB/DHHS standards for program announcements and requests for applications. NIH developed a system to upload these announcements into the Grants.gov System and provides this upload service to CDC and the Agency for Healthcare Research and Quality. To improve communications and customer satisfaction, NIH performed extensive market research for improving usability of extramural-hosted public web pages and implemented major changes that resulted in improvements to usability, appearance and format.

Streamlining Management Functions. In support of the PMA and the HHS Secretary's goal for restructuring and consolidating administrative services, a NIH Administrative Restructuring Advisory Committee (ARAC) was established to identify opportunities for streamlining NIH's management structure. The ARAC framework, with assistance from the National Academy of Public Administration, includes eight administrative management areas: Human Resources, Finance, EEO, Budget, Information Technology (IT), Grants, Facilities, and Acquisition. Examples of some of NIH's achievements including the following: Human Resources consolidated 27 separate offices into one and is using standard business practices and central data systems for electronically processing actions; EEO achieved its newly consolidated organization on October 4, 2004, resulting in one central EEO function with FTE savings of 8 percent; and the NIH IT security program has been enhanced via the establishment of a remote co-location site in Virginia to protect critical infrastructure and enhance disaster recovery.

Competitive Sourcing Program Achievements. Competitive sourcing, a key feature of the PMA, calls for Federal agencies to compete their commercial functions to determine the most cost-effective or best value service provider. NIH was identified as a "best practice" agency by the Government Accountability Office for its overall competitive sourcing program and method of selecting activities for competition. During 2004, NIH successfully completed nine competitive sourcing reviews and won eight of these competitions. NIH settled a protest to successfully resolve another review, and announced two upcoming competitions. By completing these reviews, NIH achieved a GPRA goal of conducting reviews including 274 FTEs from the Agency's commercial inventory. NIH also helped earn HHS a "green light" progress rating for the competitive sourcing portion of the PMA and move HHS from a "yellow to green" in the overall status rating, making HHS one of only five agencies to receive an overall top rating. These results culminated in the NIH Competitive Sourcing Program Manager receiving the HHS Secretary's Award for Distinguished Service and a congratulatory letter from the President.

Clinical Research Center Opening. The NIH's Mark O. Hatfield Clinical Research Center (CRC) was dedicated on September 22, 2004, and called by the namesake, a "human mosaic" embodying the vision, skills, and perseverance of many, resulting in a "new community of hope." The original Clinical Center represents 50 years of medical achievements and this center marks a new commitment to medical research providing a unique opportunity for clinicians, scientists, and patients to study and conquer both chronic and acute disease in the 21st century. This new 870,000 square foot facility will be home to new inpatient units, day hospitals and research labs, and will connect to the existing NIH Clinical Center, which opened its doors to patients in 1953. The Center provides for 242 inpatient beds and 90 day-hospital stations. This arrangement can be easily adapted to allow more inpatient beds and fewer day-hospital stations, or vice versa, as the new facility's design is highly flexible. The CRC forms the world's largest clinical research complex where NIH can continue to promote translational research — that is, the transformation of scientific laboratory research into applications that benefit patient health and medical care. The proximity of labs, equipment, and patient care units in the new CRC will help to rapidly move biomedical laboratory findings into the mainstream of medical practice — carrying on the "bench-to-bedside" tradition of the original NIH Clinical Center.

Continued Emphasis on Implementation of Unified Financial Management System (UFMS). The Unified Financial Management System (UFMS) is being implemented to replace five legacy

accounting systems currently used across the Operating Divisions (Agencies). The UFMS will integrate the Department's financial management structure and provide HHS leaders with a more timely and coordinated view of critical financial management information. The system will also facilitate shared services among the Agencies and thereby, help management reduce substantially the cost of providing accounting service throughout HHS. Similarly, UFMS, by generating timely, reliable and consistent financial information, will enable the component agencies and program administrators to make more timely and informed decisions regarding their operations. NIH requests $5.1 million to support these efforts in FY 2006.

The Program Management Office (PMO) and the Program Support Center (PSC) commenced Operations and Maintenance (O&M) activities for UFMS in FY 2004. The PMO and the PSC will provide the O&M activities to support UFMS. The scope of proposed O&M services includes post-deployment support and ongoing business and technical operations services. Post-deployment services include supplemental functional support, training, change management and technical help desk services. On-going business operation services involve core functional support, training and communications, and help desk services. On-going technical services include the operations and maintenance of the UFMS production and development environments, on-going development support, and backup and disaster recovery services. NIH requests $2.9 million to support these efforts in FY 2006.

Efficient Information Technology Management. The NIH recognizes IT as a vital resource deserving of management attention to identify areas of potential savings. A goal to consolidate key operations for improved management and cost savings was identified in the area of user support. The NIH established and met its goal of consolidating 25 IC-operated help desks into a single NIH Help Desk and, in addition, reduced the cost per ticket on the NIH Help Desk by 28 percent from FY 2003 to FY 2004, resulting in savings of approximately $3.1 million to the NIH community. In FY 2004, the consolidated NIH Help Desk processed over 273,000 requests for assistance from the NIH community, a dramatic increase over the pre-consolidation average of 80,000. Additionally, based on an industry-standard metric for help desk performance that defines first-contact resolution as either solving the user's problem or assigning it to the proper person for resolution, the NIH Help Desk has improved its first-contact resolution from 78 to 99 percent.

Care for the Environment and Physical Plant. The NIH main campus in Bethesda consists of 80 buildings sitting on 320 acres of land. As a major landlord in the bustling suburb of Washington D.C., the NIH takes seriously its commitment to tread lightly on the environment and surrounding neighborhoods. NIH developed and deployed a gas-driven steam turbine co-generation plant to reduce NIH's major emissions by 600 tons/year and to reduce greenhouse gas emissions by approximately 100,000 tons/year. Over the next 15 years, the plant will save the NIH approximately $60 million. NIH's systematic use of a Facility Condition Index to support decision-making processes over a capital facility repair program in excess of $50 million is one of two programs selected by the Department for consideration as the HHS standard.

Another step NIH is taking in FY 2006 to improve management of its research portfolio is described below.

Office of Portfolio Analysis and Strategic Initiatives. With the growth and increasing complexity of the agency, NIH has moved aggressively to transform its management strategies and decision making processes. To harmonize and better coordinate decisions that may affect the entire agency, the NIH director established in 2003 the new NIH steering committee composed of 9 institute directors. This was followed by the elimination of numerous standing or ad hoc management committees now replaced by five working groups (management and budget, extramural affairs, intramural affairs, IT, and Facilities), thus greatly streamlining the decision making process and insuring clearer accountability across all corporate agency function while preserving the autonomy of ICs in their mission specific areas.

The agency is successfully engaging in trans NIH initiatives such as the Roadmap, the Trans NIH Obesity Research Plan and the emerging Neuroscience Blueprint. It is, however, time to focus additional attention to creating better institutional tools to analyze, assess, and manage the NIH wide research portfolio and to provide better information tools to support priority setting decisions in areas of common interest to all ICs. With the growth of the agency, IC based programs need to have access to more consistent information to enable greater synergy when appropriate and to have more established mechanisms to plan their research investments, especially those which require coordination across multiple ICs. New analytic tools and systems need to be developed and implemented as part of an improved executive decision support system to improve the management of our large and complex scientific portfolio. This will allow NIH to more efficiently address important areas of emerging scientific opportunities and public health challenges. A new organizational structure will be established and staffed for this purpose.

In FY 2006, the NIH plans to create a new office within the Office of the Director—the Office of Portfolio Analysis and Strategic Initiatives (OPASI) -- which will provide tools to facilitate planning for trans-NIH initiatives, including an improved process for collecting IC data on expenditures on various diseases, conditions, and research fields, and improvements in data about burden of disease. The office will also develop, with input from the ICs, common processes and formats, where necessary, for the conduct of NIH-wide planning and evaluation. For trans-NIH planning efforts, the office will seek broad public input—from the public, health care providers, policymakers, and scientists—in addition to soliciting advice from within NIH. The office will also coordinate and make more effective use of the NIH-wide evaluation process.

PERFORMANCE ANALYSIS

Under GPRA, NIH has one program—Research. Because NIH has only one program, the "Overview of Performance" that begins on page NIH-11 also serves as the "Performance Analysis."

Research Coordination Council

Through its participation in the Department's Research Coordination Council (RCC), the NIH will continue to ensure that FY 2006 planned research, demonstration, and evaluation (RD&E) activities align with the Secretary's and President's priority areas and current RD&E activities are coordinated with other components of HHS.

NIH supports research on a range of RCC themes: Working Toward Independence; Rallying the Armies of Compassion; Protecting and Empowering Specific Populations; Realizing the

Possibilities of 21st Century Health Care; Ensuring Our Homeland is Prepared to Respond to Health Emergencies, Understanding Health Differences and Disparities—Closing the Gaps; and Preventing Disease, Illness, and Injury.

Through the RCC and participation in other meetings, the NIH will continue its commitment to support the most effective means for dissemination of science-based health information to health care providers, consumers, educators, and policy makers.

National Institutes of Health
RD&E Funding by Research Theme
FY 2006
(Dollars in Thousands)

Total Budget

Research Theme	FY 2006 Estimate
I. Working Toward Independence	$1,421
II. Rallying the Armies of Compassion	$13,796
III. No Child Left Behind	0
IV. Promoting Active Aging and Improving Long-Term Care	0
V. Protecting and Empowering Specific Populations	$12,586
VI. Helping the Uninsured and Increasing Access to Health Insurance	0
VII. Realizing the Possibilities of 21st Century Health Care	$22,381
VIII. Ensuring our Homeland is Prepared to Respond to Health Emergencies	$393,820
IX. Understanding Health Differences and Disparities—Closing the Gaps	$47,457
X. Preventing Disease, Illness, and Injury	$600,897
XI. Agency-Specific Priorities 1/	27,485,526
Subtotal, Research	28,577,884
B&F	81,900
Total Budget	28,659,784
Superfund	80,289
NIH Progam Total	28,740,073

1/ Other Programs - Includes grants, intramural, other R&D contracts, RMS
Includes $150,000 M for Type 1 Diabetes Research in FY 2005 and FY 2006.

FY 2005 Health IT Initiative

The President has established a goal to make secure Electronic Health Records (EHRs) available to the majority of Americans. To accomplish this, a variety of concomitant challenges and barriers must be addressed. In FY 2005, under the authority of Section 208 of the Departments of Labor, Health and Human Services, and Education, and Related Agencies Appropriations Act, 2005, $9.349 million will be transferred among the NIH Institutes and Centers to the National Library of Medicine (NLM), which will be combined with $151,000 from the NLM. Working together with the Office of the National Health Information Technology Coordinator (ONCHIT), NLM will accelerate the development of interoperability standards and prototypes for the secure exchange of electronic health records. Prototypes will be developed through contracts to public-private consortia that will demonstrate the ability to build and operate the National Health Information Network (NHIN). In recent years, NLM has funded important standards development and implementation initiatives through its other programs and will play an important role as a collaborator with HHS in ensuring the adoption of standards to create an interoperable NHIN.

FY 2006 BUDGET POLICY

The FY 2006 program level for the NIH is $28,845 million, an increase of $196 million or 0.7 percent over the FY 2005 Appropriation. The NIH's President's Budget authority request to the Labor/Health and Human Services/Education Appropriations Subcommittee is $28,510 million, an increase of +$145 million and 0.5% over the FY2005 level. The budget authority request to the Veteran's Administration/Housing and Urban Development Appropriations Subcommittee is $80.3 million for the NIEHS Superfund research program. The NIH program level also includes $150 million for the Type I Diabetes Initiative appropriated by Public Law 107-360. Of this program total, $97.1 million is included in the budget authority request of the Public Health and Social Services Emergency Fund (PHSSEF), for research in radiological/nuclear/chemical countermeasures.

In this budget request, NIH provides resources in the RPG mechanism to preserve to the greatest extent possible the ability of scientists to obtain individual support. NIH will continue to sustain efforts such as the Roadmap for Medical Research and the Neurosciences Blueprint that provide, on a competitive basis, new opportunities for scientific advances by developing novel resources and supporting interdisciplinary innovations that will enhance the scientific reach of individual researchers. The NIH will also continue to invest in high-quality research spanning the entire spectrum of NIH's Institutes and Centers, such as AIDS, Biodefense, cancer, diabetes, etc.

NIH Roadmap for Medical Research

NIH has embarked on an ambitious program to refocus the investments made during the doubling period, to help us move from 20th century medicine to 21st century medicine, and to coalesce the research community around a strategic initiative—the NIH Roadmap.

In FY 2006, NIH will direct $333 million towards the Roadmap initiatives, an increase of +$97.5 million over the FY2005 Appropriation. Of this amount, $83 million will be provided by the NIH Director's Discretionary Fund (DDF), and the remaining $250 million will be provided by the Institutes and Centers (ICs). The IC contribution to support these trans-NIH research goals is estimated to be 0.9 percent of each individual budget request for FY 2006.

The funding level for New Pathways to Discovery is $169 million, funding for Research Teams of the Future is $44 million, and funding for Re-engineering Clinical Research is $120 million. More detailed information on the funding levels for the NIH Roadmap is shown on pages NIH-26-32.

NIH Blueprint for Neuroscience Research

NIH will implement its "Neuroscience Blueprint" that is serving as a framework to enhance the effectiveness of the NIH neurosciences research agenda, which is supported by 15 Institutes and Centers. Advances in the neurosciences and the emergence of powerful new technologies offer many opportunities for Blueprint activities that will enhance the effectiveness and efficiency of neuroscience research. Over the past decade, driven by the science, the NIH neuroscience Institutes and Centers have increasingly joined forces through initiatives and working groups focused on specific disorders. The Blueprint builds on this foundation, making collaboration a day-to-day part of how the NIH does business in neuroscience. By pooling resources and expertise, the Blueprint can take advantage of economies of scale, confront challenges too large for any single Institute, and develop research tools and infrastructure that will serve the entire neuroscience community.

In FY 2005, participating Blueprint Institutes and Centers are developing an inventory of neuroscience tools funded by NIH and other government agencies, enhancing training in the neurobiology of disease for basic neuroscientists, and expanding ongoing gene expression database efforts, such as the Gene Expression Nervous System Atlas (GENSAT).

In FY 2006, NIH allocated $12 million for Blueprint initiatives as follows:

- developing genetically engineered mouse strains specifically for nervous system disease research ($2.0 million);
- training in critical cross-cutting areas such as neuroimaging and computational biology ($2.5 million); and

- supporting specialized, interdisciplinary "core" centers that might focus on areas such as animal models, cell culture, computer modeling, DNA sequencing, drug screening, gene vectors, imaging, microarrays, molecular biology, or proteomics and their applications to neuroscience research ($7.5 million).

The 15 collaborating Institutes and Centers will contribute an additional $14 million, for a total of $26 million for this initiative in FY2006.

AIDS

The AIDS research program would increase by 0.4 percent or $12 million, for a total of $2,933 million. The FY 2006 NIH AIDS Research budget estimate places the highest priority on the goal to develop an AIDS vaccine. This includes programs focused on the discovery, development, pre-clinical, and clinical testing of HIV vaccine candidates. The evaluation of an AIDS vaccine will require extensive testing in the United States and in international settings. Included in the AIDS estimate is $34 million to support the expansion of the Global HIV Vaccine Enterprise, a virtual consortium to accelerate HIV vaccine development, announced at the G-8 summit in June, 2004. NIH will also continue to support the Global Fund for HIV/AIDS, Malaria and Tuberculosis, by providing $100 million from its total budget in FY 2006.

Biodefense

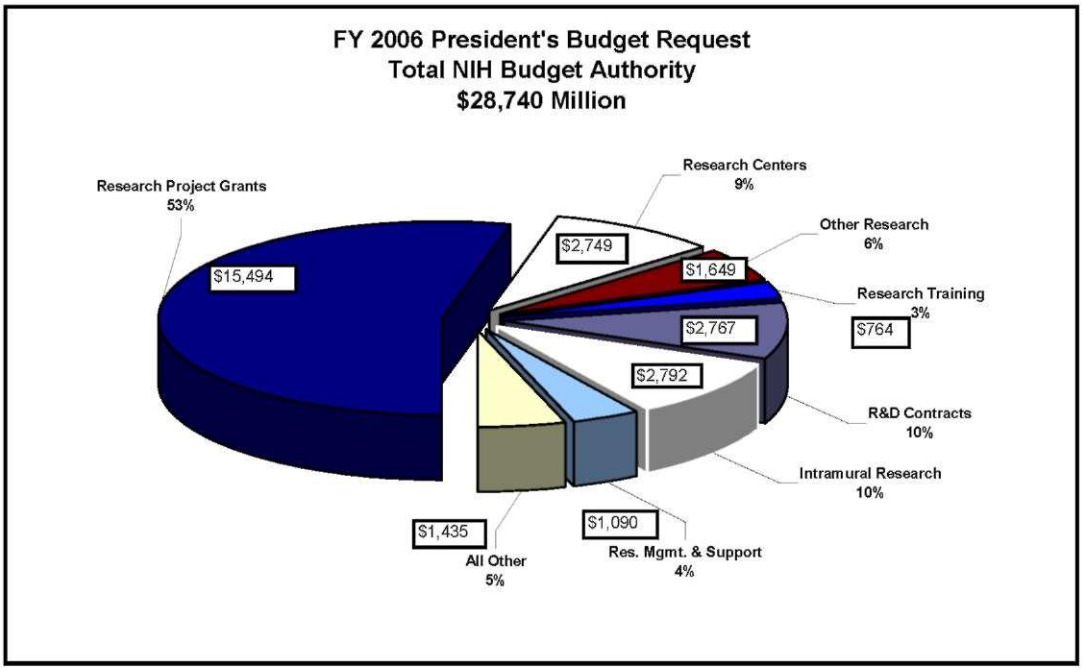
NIH will continue implementation of the long-range strategic plan for biodefense research. The NIH total Biodefense budget level is $1,694 million, an increase of $6 million over the FY 2005 estimate. When adjusted for one-time extramural facilities construction in FY 2005, however, research activities in the biodefense research program will increase by $125 million and 8.1 percent.

Biodefense Research priorities in FY 2006 include:

Clinical development of vaccines for plague, tularemia, Valley Fever, Ebola, botulism, and West Nile Virus

Clinical development of anti-toxin/antibody treatment for anthrax

Preclinical development of drugs, vaccines, and diagnostics with a focus on therapies (Partnership grants with industry, research resources for anti-infectives)
Initiate the third phase of construction of specialized, high-containment research laboratories for extramural researchers. These specialized research laboratories, at the BSL-3 and -4 levels, are necessary to conduct research on the highly dangerous and infectious pathogens in the biodefense research field. The laboratories are a critical component of the planned network of extramural Regional Centers of Excellence.



Mechanism Discussion

The funding of basic biomedical research through investigator-initiated research, including Research Project Grants (RPGs), and ensuring an adequate number of new researchers with new ideas remain a high priority for the National Institutes of Health. The FY 2006 President's Budget would support an estimated 9,463 competing RPGs, for $3.6 billion, an increase of an estimated 247 competing RPGs from the FY 2005 Appropriation. The average cost of a competing RPG is $377 thousand. This cost is skewed, however, by an extremely large cohort of AIDS clinical trials cycling from noncompeting into competing status (102 awards, average cost $2.8 million per award), as well as the extremely large G-8 HIV Vaccine awards (14 awards, average cost $2.4 million per award.). When adjusted for this large cohort of AIDS grants, the average cost for a competing RPG is $347 thousand. While no inflationary increases are provided for direct, recurring costs in non-competing RPG's, where the NIH has committed to a programmatic increase in an award, such increases will be provided.

Research Centers increases by +$62 million, or 2.3 percent over the FY2005 appropriation, as a result of program increases for the Roadmap, Biodefense, AIDS, and the Neuroscience Blueprint research activities.

Other Research increases by +$6 million, or 0.4 percent, again, as a result of program increases for the Roadmap, Biodefense, and AIDS research activities.

In order to achieve the NIH's research objectives, it is essential to ensure that highly trained scientists will be available to address the nation's biomedical, behavioral and clinical research needs. The NIH has been working in a measured and deliberate way to

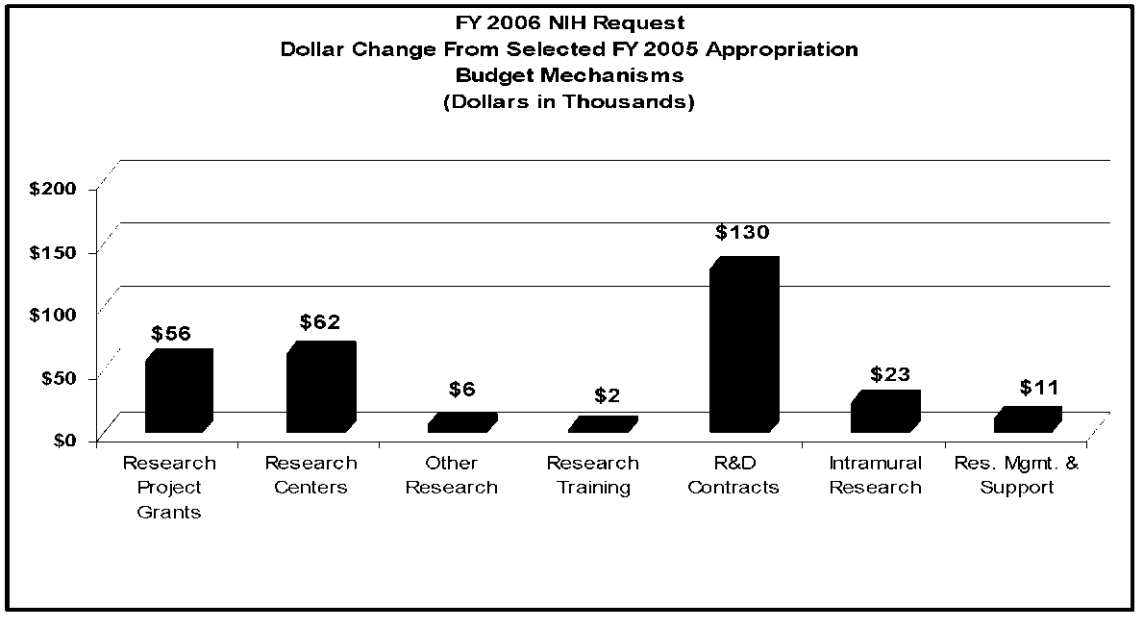
adjust current stipends for the Ruth L. Kirschstein National Research Service Awards (NRSAs) upwards to $45,000 for entry-level postdoctorates. These stipend targets were developed in coordination with the National Academy of Sciences and have been embraced by universities and professional organizations. In the FY 2006 request, most stipend levels for individuals supported by the Ruth L. Kirschstein National Research Service Awards are maintained at the FY2005 levels. To help prevent the potential attrition of our next generation of highly trained post-doctoral trainees, stipend levels for post-docs with 1-2 years of experience are increased by 4.0%. Stipends for postdoctoral fellows which ranged from $35,568 to $51,036 in FY 2005 depending on years of experience, would increase to a range of $36,996 to $51,036. This will bring these stipends closer to the goal NIH established for post-doc stipends in March, 2000. In addition, individual post-doctoral fellows will receive an increase of $500 in their institutional allowance for rising health benefit costs. The need for increased health benefits is particularly acute for these post-doctoral trainees, who, because of their age and stage of life are more likely to have family responsibilities. The increases in stipends and health insurance are financed within the FY 2006 request by reducing the number of Full-Time Training Positions, because NIH believes that it is important to properly support and adequately compensate those who are participating in these training programs, so that the programs can continue to attract and retain the trainees most likely to pursue careers in biomedical, behavioral and clinical research. NIH will support a total of 17,442 FTTPs for $764 million, a decrease of -397 FTTPs from the FY 2005 Appropriation.

Research and Development (R&D) contracts increase by +$130 million and 4.9 percent compared to the FY 2005 Appropriation. The majority of this increase is for Biodefense R&D contracts (+$108 million, or 19 percent), but other significant programmatic increases are included for AIDS (+$14 million), and the Roadmap (+$3 million).

Intramural Research increases by $23 million. Research Management and Support increases by $11 million.

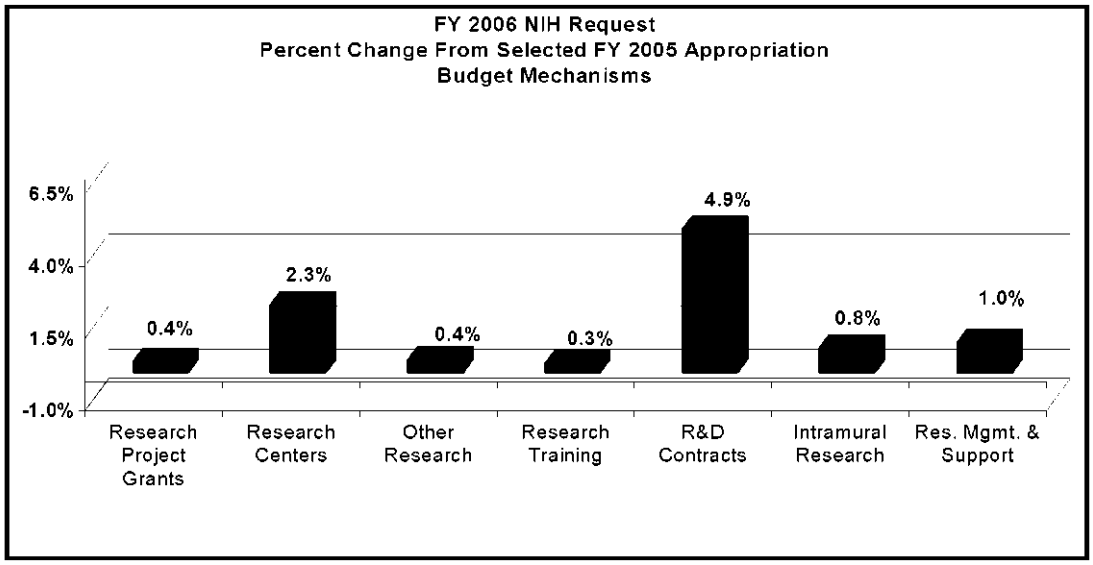
An integral element to developing and supporting a robust extramural biodefense research program in the U.S. is to build and provide to extramural researchers the use of the specialized, high-containment labs that they need in order to conduct research on the most dangerous and infectious pathogens known to exist. Researching these pathogens requires the use of biosafety level (BSL) 3 and/or BSL-4 research laboratories. These specialized facilities, in conjunction with specialized procedures, are designed to eliminate the threat to laboratory and clinical personnel, and to adjacent communities, of these highly-lethal and infectious agents. In FY 2006, NIH is requesting a total of $30 million. Consistent with the FY 2005 President's Budget request, no funds are provided for non-biodefense extramural construction.

In the FY 2006 President's Budget, B&F would be funded at $90 million. Of this amount, $8 million would be provided to the National Cancer Institute (NCI) for repairs and improvements at the NCI-Frederick campus. The remaining $82 million will allow



NIH to fund ongoing programs for essential safety and regulatory compliance, as well as Repairs and Improvements, in order to maintain valuable research capacity and to ensure the safety of NIH facilities and their occupants.

The Office of the Director (OD) increases by $27 million, or 7.6 percent. Of this amount, $83 million has been reserved in the NIH Director's Discretionary Fund for the NIH Roadmap for Medical Research, an increase of +$23 million over the FY2005 Appropriation. The increase for the OD excluding Roadmap funding is $4 million or 1.3 percent



Other Key Issues

Nuclear/Radiological/Chemical Countermeasures Research
The use of a nuclear or radiological device in a terrorist attack presents a critical challenge to the United States. The most plausible terrorist radiological or nuclear scenarios envision situations that are more limited in scope and in which the health effects of radiation exposure could be mitigated by intensive medical intervention. In FY 2006, NIH will continue its research efforts in nuclear/radiological countermeasures, focusing on:

- the development of drugs that can be used to prevent injury from radiological exposure;
- improved methods of measuring radiological exposure and contamination (biodosimetry); and
- the development of methods/drugs to restore injured tissues and eliminate radioactive materials from contaminated tissues (i.e., drugs that could scavenge radionuclides from tissues).

The use of toxic chemicals and chemical warfare agents as a Weapon of Mass Destruction (WMD) is also of concern because of the availability of many hazardous chemicals and their high toxicity. The most likely public scenarios in which chemicals could be used are: deliberate attacks at chemical plants, storage facilities, or chemical transport vehicles; release of chemical agent(s) in public settings; use of improvised devices combining chemicals with explosives; and contamination of food or water.

In FY2006, NIH will initiate a concerted effort to address those chemical threats posing the greatest risk to civilian populations in the U.S. Leading chemical threats to civilian populations include: nerve agents (primarily inhaled organophosphates), cyanide (inhaled and ingested hydrocyanic acid and cyanogen chloride), and toxic industrial chemicals (especially those inducing pulmonary edema, such as chlorine, phosgene, and ammonia).

This research effort includes three broad elements:

- basic research to address critical gaps in knowledge important to the development of medical countermeasures;
- evaluation of the mechanisms of injury and the host response, and the enhancement of the repair process; and
- the evaluation and development of promising countermeasures. In addition, research objectives for this program include the establishment of several research centers of excellence, the development of appropriate animal models, the identification of medical products near IND approval or licensure, and the development of improved diagnostic tools.

The Department of Health and Human Services (HHS) has requested that a total of $97.1 million be provided in FY 2006 to support specific targeted research activities needed to develop radiological/nuclear ($47.1 million) and chemical threat ($50.0

million) countermeasures. While NIH would manage and oversee this work, these funds are budgeted in the Public Health and Social Services Emergency Fund (PHSSEF). Placing these funds in the PHSSEF enables them to be appropriated in one place, as with some other biodefense funds in the DHHS, and then allocated to the proper NIH Institutes or Centers to implement the targeted activities. In addition, NIH will continue to collaborate closely with research centers in other federal agencies. For example, recent collaborations have included interagency agreements that supported the Armed Forces Radiobiology Research Institute (AFRRI) to expand their radiobiology and radiological/nuclear defense research and an interagency agreement with the U.S. Army Medical Research and Materiel Command to renovate a specialized laboratory to support future military-civilian chemical defense research.

IT Systems

Included within the overall budget amount is continued funding for four NIH-wide "Enterprise" Information Technology projects: Electronic Research Administration (eRA) for grants processing; the NIH Business System for a wide-range of financial and other administrative functions; the NIH portion of the HHS Enterprise Human Resources and Payroll system (EHRP); and the Clinical Research Information System (CRIS).

NIH's budget for FY 2006 includes funding to support the President's Management Agenda e-Gov initiatives and Departmental enterprise information technology initiatives. NIH funds will be combined with resources in the Information Technology Security and Innovation Fund to finance specific information technology initiatives identified through the HHS strategic planning process and approved by the HHS IT Investment Review Board. These enterprise Information Technology investments promote collaboration in planning and project management and achieve common goals such as secure and reliable communication and lower costs for the purchase and maintenance of hardware and software. Examples of HHS enterprise initiatives currently being funded are Enterprise Architecture, Enterprise E-mail, Network Modernization, and Public Key Infrastructure.

NIH Management

The Scientific Review and Evaluation Award (SREA) Program provides peer reviews for nearly 75,000 grant applications through extramural awards to the Chairpersons of the various Initial Review Groups. These reviews are indispensable to NIH's grant application review process and are a critical component to our scientific mission.

This program is currently funded by extramural funds to cover program oversight and honoraria and transportation and per diem allowances for the reviewers. In FY 2006, NIH will complete a modernization of this process. These changes in the administration and management of the program and related processes will strengthen internal controls, oversight and accountability. A comparable adjustment of $55 million in FY2005 is shown in this budget request, shifting the funding for this program from Other Research Grants to RMS.

The FY 2006 request includes $2.0 million in the Office of the Director for the Office of Portfolio Analysis and Strategic Initiatives (OPASI). The OPASI will develop and apply analytic tools to review the research portfolio in selected areas of science; report on funding for selected diseases and areas of science using improved analytic systems, and systematically monitor public health need/burden of disease.

The workforce at NIH is one of its greatest assets because of the large numbers of staff and their great diversity of qualifications, disciplines, types of appointments, and levels of expertise. This array of talent and systematic interdependence of scientific, programmatic, and administrative staff and missions has helped create NIH's success and its reputation as one of the world's leading biomedical research organizations. As the nature of science continues to change, the tools of administering that science must also change. NIH must ensure that it continues to meet these new opportunities with the best tools to attract and retain its staff, ensure the needed talent and skills, and plan for its future workforce needs. NIH will continue to require personnel to manage the research portfolio and recruit the best scientists to conduct world-class research. In FY 2006, at the HHS Planning Level, NIH is requesting 17,547 FTEs, an increase of 4 FTEs over the FY2005 Appropriation. These FTEs will support the National Science Advisory Board for Biosecurity.

FULL-TIME EQUIVALENTS (FTEs)

	FY 2004 Enacted	FY 2005 Appropriation	FY 2006 Estimate	Change FY 05 Approp./ Request
Ceiling	**17,073**	**17,533**	**17,537**	**4**
Ceiling Exempt	**20**	**10**	**10**	**0**
Total NIH	**17,093**	**17,543**	**17,547**	**4**