NARRATIVE BY ACTIVITY

Authorizing Legislation: Section 301 and Title IV of the Public Health Service Act, as amended

National Institutes of Health

(dollars in millions)

	FY 2005 Actual 1/2/	FY 2006 Appropriation 3/	FY 2007 Estimate	Increase or Decrease
Program Level 4/ 5/ 6/.....	$28,653	$28,587	$28,587	$0
Total NIH B. A. 5/ 6/.....	28,644	28,578	28,578	0
Labor/HHS Budget Authority ..	28,415	28,349	28,350	1

1/ Comparable for nuclear/radiological countermeasures research funded through the PHSSEF
2/ Comparable for transfers to Global Fund for HIV/AIDS, Tuberculosis and Malaria
3/ Comparable for Pandemic Influenza activities funded through the PHSSEF
4/ Includes $8.2M from the Program Evaluation set-aside
5/ Includes funds to be requested from Interior for the Superfund Research program.
6/ Includes funds for Type I Diabetes Initiative

This document provides justification for the Fiscal Year 2007 activities of the National Institutes of Health

Performance Analysis

Under GPRA, NIH has one program—Research. Because NIH has only one program, the "Overview of Performance" provides most of the information expected in the "Performance Analysis" section of this Performance Budget. For example, the Overview includes "Significant Accomplishments of Performance Goals" and other information about the two goals highlighted in the table below.

Representative NIH Performance Goals in the HHS Annual Plan

Performance Goal	Results	Context
By 2012, develop a knowledge base on chemical effects in biological systems using a systems toxicology or toxicogenomics approach.	NIH established this goal in FY 2003 and has met the annual targets toward the goal in each year since then. In FY 2005, NIH created and provided public access to a database of information on chemicals found in the environment and drugs that have an effect on biological	This performance goal is about predicting potential human health risks by examining how chemical exposures disrupt biological processes at the molecular level. NIH is establishing a knowledge base on Chemical Effects in Biological Systems (CEBS) to enable predicting the effects on human health from chemicals about which little is known. The system will contain data on global gene expression, protein

	systems. The database includes information on molecular expression and toxicology/pathology.	expression, metabolite profiles, and associated chemical/stressor-induced effects in multiple species.
By 2005, create the next generation map of the human genome, a so-called haplotype map ("HapMap"), by identifying the patterns of genetic variation across all human chromosomes.	NIH established this goal in FY 2003, met the annual targets toward the goal in each year since then, and completed the goal in 2005.	This performance goal is about developing a tool that researchers can use to find the genes and variants that contribute to many diseases or disease risk. NIH has taken a leadership role in the development of the HapMap, a catalog of the DNA "blocks" or haplotypes and the identifying SNPs (single nucleotide polymorphisms), sites in the genome where individuals differ in their DNA spelling by a single letter. NIH has completed the goal by developing a first-pass draft HapMap with 1.007 million SNPs.

In FY 2007 the NIH Buildings and Facilities Program and the Intramural Research Program were reviewed through the PART process. Both programs were deemed *Effective, with scores of 96 percent and 90 percent respectively.* On the FY 2006 PART, the NIH Extramural Research Program achieved a similarly high 89 percent. These scores demonstrate exemplary management and ample progress toward meeting NIH performance measures including goals for Scientific Research Outcomes and for Capacity Building and Research Resources. For follow-up actions, programs will continue to practice good management, to enhance the presentation of budget-performance integration, and to annually progress toward meeting long-term performance goals.

Rationale for Budget Request

INTRODUCTION

The Nation's substantial investment in NIH is yielding innumerable scientific achievements, which are helping to improve the length and quality of human life. Research is contributing to the reduction in morbidity and mortality from heart disease, stroke, cancer, and infectious disease. The research NIH conducts and supports today will be the basis for countless future advances in science and improvements in health. Such research ranges from rigorous multicenter clinical trials for testing new therapies to the transformation of day-to-day medical practice through practical applications in genomics.

Today, in large part because of the success of medical research, our citizens are living longer than ever before. However, 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 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 disease, Alzheimer disease, hypertension, and cancer. At the same time, acute infectious diseases, such as strains of influenza that have pandemic potential, antibiotic resistant tuberculosis, and infectious agents that might be used for bioterrorism remain a continuing and evolving challenge. And the Nation also faces significant health disparities among racial, ethnic, and disadvantaged populations.

NIH-funded research programs are unique in both igniting and complementing private sector research and development efforts. NIH tackles research essential to public health, 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.

Despite the agency's wide range of responsibilities to the public health, NIH must remain nimble and responsive to new opportunities and challenges. For example, NIH continues vigorous implementation of the NIH Roadmap for Medical Research—a set of cross-cutting initiatives responding to emerging scientific needs and opportunities. To strengthen the clinical research enterprise, NIH just launched the Clinical and Translational Science Award (CTSA) program. The CTSA program is an unprecedented effort to create the human and physical infrastructure necessary for rapidly and efficiently translating basic research discoveries into better treatments for patients. More recently, NIH established a new office that will strengthen the agency's priority-setting processes and capacity for collaboration and program evaluation across Institutes and Centers.

To maintain the vibrancy of our Nation's scientific enterprise, NIH actively supports strong basic and clinical research training programs. NIH is augmenting its strategies to support the independence of young investigators. This includes a new career transition award program that will promote the initiation of independent research careers. NIH also will expand the use of the best practices currently employed by NIH Institutes and Centers to foster new investigator independence.

The text below highlights a few of the major areas of research in the NIH research portfolio, including a sampling of the most significant scientific discoveries from the past year and highlights of initiatives planned for FY 2007. 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. The scientific advances reported in the following pages are the outcome of many and varied investments in medical research by NIH, some of which began more than a decade ago.

MEDICINE IN THE 21ST CENTURY: PREDICTIVE, PERSONALIZED, AND PREEMPTIVE

Through strategic investments in advanced technologies and their application, NIH strives to implement a fundamentally new paradigm for biomedical research in the 21st century. The paradigm aims to tackle diseases through a rationally designed multipronged approach that addresses the complete cycle of a disease process. The ultimate goal is drastic improvements in health care.

This new paradigm is predictive, personalized, and preemptive:

- Predictive medicine uses molecular information to identify the potential for disease in a patient before symptoms occur.

- Personalized medicine identifies disease risk and customizes treatments on an individual, patient-by-patient basis.

- Preemptive medicine intervenes in the disease process before symptoms ever appear in order to preserve normal function and potentially obviate progression to disease entirely.

For example, age-related macular degeneration (AMD) is a common eye disease associated with aging that gradually destroys sharp, central vision. AMD affects nearly 30 percent of those over age 75. NIH researchers discovered a nutritional supplement that *preempts* the development of AMD. The new supplement could protect 300,000 of the estimated 1.3 million Americans who will develop advanced AMD in the next 5 years. Additional research identified a gene, "complement factor H," which is strongly associated with an individual's risk for developing AMD. This discovery may lead to new tests that *predict* an individual's risk for AMD, and additional new strategies for disease preemption.

Regarding *personalized* treatment, researchers identified a panel of 16 genes that can be tested using a tumor sample from each breast cancer patient. The sample is tested for mutation in each of the 16 genes. The test result gives a recurrence score that predicts what treatment the patient will benefit from most, hormonal therapy or chemotherapy. This personalized test will allow 100,000 women a year to make a more informed treatment choice and improve the quality of life of approximately 70,000 women who will not needlessly undergo chemotherapy. (Also see the Story of Discovery, "Pharmacogenetics Leads the Way to Personalized Medicine" in the "Advances in High Tech Medicine" section below.)

These examples illustrate how basic research, using cutting-edge technologies, has the potential to transform 21st century medicine. Another example of such a paradigm-shifting technology is RNA interference (RNAi), which allows researchers to turn off specific genes in specific cells. The technology is moving toward clinical applications. Recently, NIH researchers created an RNAi that was able to block the viral RNA that causes cervical cancer. With further studies, such a therapy could develop into a new treatment for cervical cancer.

GENES, ENVIRONMENT, AND HEALTH INITIATIVE

Virtually every disease has both a hereditary and an environmental component that determines its effect on a given individual. Through this new initiative, NIH is exploring the relative contributions of the two components in onset and progression of 10 diseases with substantial public health impact—disorders such as heart disease, diabetes, cancer, stroke, Alzheimer disease, schizophrenia, osteoporosis, asthma, cataracts, hypertension, Parkinson disease, autism, and obesity.

The Hereditary Component: Genetics

Inherited traits are transmitted from parent to child through the 3 billion DNA letters that make up the human genome. Within that massive instruction book, about 10 million alternate spellings, or "variants," make up the genetic differences among individuals, and dictate the genetic predisposition to get or resist disease. Researchers studying individual diseases need to know exactly which of the 10 million variants correlate with their disease of interest. However, measuring (or "genotyping") all 10 million variants in each patient are prohibitively expensive. A recently developed shortcut will help.

Variation in the human genome is organized into local neighborhoods, called haplotypes, that usually are inherited as intact blocks of information. By studying genetic inheritance in terms of haplotypes, instead of individual variants, researchers get almost 100 percent of the information, at just one-fortieth the cost in terms of time, effort, and resources. The NIH led an international consortium (http://www.hapmap.org) to develop the HapMap (haplotype map), a catalog of these blocks of genetic variation. Researchers have already used the HapMap to find the genes and variants that contribute to common diseases like macular degeneration, Parkinson disease, cardiac arrhythmia, and celiac disease.

The next step is to systematically examine large collections of patients and matched controls, for a wide variety of common diseases, to look for patterns in the HapMap. For many diseases, prior investments have created significant repositories of patient records and DNA samples. Using the new tool for genetic analysis created by the HapMap, NIH researchers should be able to capitalize on those prior investments, and greatly accelerate their progress in determining genetic risk factors, and prevention strategies, for dozens of diseases.

The Environmental Component: Exposures and Behavior

Recent "epidemics" of diseases like diabetes, childhood asthma, and obesity cannot be due to major shifts in the human genome (which occur over tens or even hundreds of thousands of years), but must be due to more recent environmental, dietary, and behavioral changes that produce disease in genetically predisposed persons. This initiative, therefore, also includes investment in innovative new technologies, including small wearable sensors that measure environmental agents in the air as it is inhaled and internal devices that measure changes in proteins and other substances in blood in real time during eating and other activities. Correlating these data with states of disease and health will further enable researchers to dissect the interplay between genetic and environmental components in disease, in order to craft better strategies for improving public health.

NEW INVESTIGATORS

Data indicate that the average age of first-time (new) Principal Investigators obtaining R01 research funding from NIH has risen to 42 years for Ph.D. degree holders and 44 years for M.D. and M.D./Ph.D. degree holders. This trend must be curtailed in order to capture the creativity and innovation of new independent investigators in their early career stages to address our Nation's health-related research needs. The National Research Council of the National Academies of Science issued two reports in 2005 about research training and career development—*Bridges to Independence: Fostering the Independence of New Investigators in Biomedical Research* and *Advancing the Nation's Health Needs: NIH Research Training Programs.* Both reports call for action now. To this end, the NIH Director formed a New Investigators Committee, co-chaired by the NIH Deputy Director for Extramural Research and the Director of the National Institute of Neurological Disorders and Stroke. The Committee developed a list of action items that will facilitate an investigator's ability to receive his/her first independent R01 award earlier in his/her research career.

A key recommendation is to develop and implement a new career transition award program that will promote the initiation of independent research careers. The award will provide up to 5 years of support in two phases. The initial phase will provide 1-2 years of mentored support. That phase will be followed by 1-3 years of independent support, as long as the recipient secures an independent research position. NIH's intent is for award recipients to compete successfully for independent awards during the career transition award period. NIH also plans to expand the use of the best practices currently employed by NIH Institutes and Centers to foster new investigator independence. These practices include more generous paylines, and the special consideration of applications from new investigators. In addition, the Center for Scientific Review, the NIH unit

that evaluates the majority of NIH investigator-initiated grant applications, aims to reduce the time from application submission to notification of review for new investigators so they can resubmit a revised application by the next submission deadline. Finally, NIH plans to develop processes and systems to identify, enumerate, and track all predoctoral and postdoctoral researchers supported by NIH regardless of funding mechanism. This will enhance the agency's ability to make more informed programmatic decisions regarding all new investigators and enhance monitoring their progression toward research independence.

NIH ROADMAP FOR MEDICAL RESEARCH

Launched in September 2003, the NIH Roadmap for Medical Research serves as a test bed for high-risk, enabling and emerging scientific opportunities. This innovation in the management of biomedical research is designed to accelerate the pace of discovery and improve the translation of research findings into medical and health interventions for public benefit. The Roadmap currently 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. Each theme is executed by a team of working groups, each carrying out multiple initiatives designed either to fill gaps in the American biomedical research program, or to help incorporate new technologies and trends into the NIH of the new millennium.

Having completed its second year of funding implementation, some initiatives are rapidly progressing toward their goals, while other endeavors will take longer to come to fruition. All the efforts of the NIH Roadmap are designed to respond to the needs of the biomedical research community. Many have changed the way that NIH does business. The Roadmap is using a number of mechanisms to accomplish its goals—from R01 grants to the creation of new Centers. Examples of NIH Roadmap initiatives, by theme and working group, are highlighted below.

New Pathways to Discovery

Initiatives under the NIH Roadmap's *New Pathways to Discovery* theme are pushing the envelope of possibility with cutting-edge technologies—working at smaller and smaller scales down to the atomic level, processing information at faster and faster speeds, and synthesizing huge data sets from disparate fields, all in ways barely imaginable a decade ago.

Molecular Libraries and Imaging. Small molecules are extremely important to researchers who explore function at the molecular and cellular levels, and to clinicians who treat disease. For almost every microscopic structure in a cell, a few small molecules will bind to it. After they bind, some (like most drugs) may block the function of the structure, others may actually increase the function of the structure, while others have no effect at all. These inactive small molecules can be tagged with fluorescent dyes that can light up the structure under a microscope, allowing researchers to visualize movement and function in real time. This is a potent tool to identify mechanisms of protein trafficking and genetic regulatory networks. A key challenge is to identify the small molecules that bind the right targets and have the desired biological effects. Through the a process of high-throughput screening (HTS), researchers can systematically screen tens, or even hundreds, of thousands of small molecules to find a successful match between a

chemical and its target. However, preserving banks of hundreds of thousands of molecules, keeping them organized and accessible, and maintaining the facilities, machinery, and expertise needed to screen them at the molecular level, is extremely expensive and almost impossible for any individual researcher to do. The NIH is taking the lead as a repository and resource for researchers needing to tap into this exciting new opportunity for discovery. Selected Molecular Libraries and Imaging initiatives are described below:

Building Blocks, Pathways and Networks. In initiatives from this NIH Roadmap working group, researchers focus on the development of new technologies to accelerate discovery of biological pathways and networks. In the past, our limited understanding of complex biological systems, and limitations on the technological capabilities to study them, led researchers to focus on simple systems—individual molecules or cells outside their normal contexts. More recently, researchers have come to understand the interdependence of various processes and the tight feedback systems and balances that exist in nature. A subtle change in the relative concentration of a single hormone may lead to a dramatic and devastating effect on a person's well-being. Comprehensive study of these intricate and interconnected pathways will facilitate our understanding of the communication among genes, molecules, and cells that is so important in biological function and avoidance of disease.

Bioinformatics and Computational Biology. In recent years, biomedical research has developed extraordinarily powerful data generation methods, such as digital imaging and automated DNA sequencing. This has generated an enormous wealth of data that needs to be mined with powerful tools. The goal of the Bioinformatics and Computational Biology Roadmap initiative is to create a national biomedical software engineering system to do just that. In FY 2005, the NIH Roadmap funded three new National Centers for Biomedical Computing (NCBCs). Together with the four Centers that NIH funded in FY 2004, these Centers will serve as the core of a universal computing infrastructure, allowing researchers and physicians in the biomedical community to seamlessly integrate, analyze, model, and share data on human health and disease.

***Nanomedicine*.** Nanotechnology is the study and manipulation of objects at the "nano" level—one-billionth of a meter, the scale of individual proteins. Recent advances in engineering, microscopy, and computing have enabled scientists to push the boundaries of exploration down to near-infinitesimal scales, opening up opportunities for discovery impossible just a decade ago. The Nanomedicine Initiative seeks to apply the principles and techniques of nanotechnology to biological systems: studying single molecules and their interactions, making measurements, and using mathematical and analytical tools to achieve a more fundamental understanding of biochemical processes and disease. The initiative uses such knowledge to drive the design of new nanomachines and devices that may interact with living systems to improve human health. The four teams awarded in FY 2005 will study and manipulate proteins being folded into functional forms inside cells; attempt to harness the ability of cell membranes to build new power sources for cells and construct miniature prosthetic devices; and observe and measure molecular movements and force generation–processes that are so important in cellular function and repair. This research could lead to production of engineered cells whose movement can be programmed and to a deeper understanding of the way cells interact with each other and with their environment.

Structural Biology. Membrane proteins (proteins that exist embedded in or attached to the surface of a cell or one of its internal compartments) are vital to health and comprise about one-third of all human proteins. They control the movement of molecules into and out of cells and mediate critical activities like nerve impulses and immune responses. Defects in membrane proteins cause a host of diseases, and a large number of drugs target membrane proteins. Clearly, improving the understanding of membrane proteins could shed light on myriad biological processes and dramatically advance the ability of doctors to detect, treat, and prevent disease. Because membrane proteins need to be anchored in a membrane to function normally, they cannot simply be produced in a flask or mixed up in a test tube like ordinary proteins. This makes them more challenging to study. In FY 2004, the NIH Roadmap funded two Centers for Innovation in Membrane Protein Production, with the goal of developing novel approaches to preparing membrane proteins that are structurally and functionally intact. To further improve and accelerate structural biological studies of membrane proteins, the 2005 initiative "Membrane Protein Production and Structure Determination" awarded one 5-year program project grant, nine 5-year research grants, and eight 2-year exploratory, "high risk/high impact" projects.

Research Teams of the Future

As the cumulative store of scientific knowledge continues to expand exponentially, scientists increasingly must focus and specialize to push their fields to new heights. However, as noted above, researchers also increasingly appreciate the importance of the interactions and interconnectivity within biological systems. This reality, in addition to the scale and complexity of today's biomedical research problems, requires today's researchers to extend themselves beyond their own areas of research to thrive in collaborative science teams and new scientific disciplines. *Research Teams of the Future* encourages new ways of combining skills and disciplines; training of investigators to thrive in interdisciplinary settings; and development of novel support mechanisms to facilitate these endeavors.

Major Policy Change to Recognize Multiple Principal Investigators. Traditionally, each NIH research project had a single leader, or Principal Investigator (PI). However, this became a significant barrier to the interdisciplinary team approach that is critical for modern research. Because the careers of individual investigators hinge upon their ability to acquire individual funding for their research, restricting recognition to a single PI discourages collaborative team research. When the Interdisciplinary Research Working Group of the NIH Roadmap convened in early 2003, it adopted a recommendation to recognize and credit more than one PI on a research grant. To help meet this challenge, the Deputy Director for Extramural Research established a work group to plan and implement the changes in NIH regulations, application forms, data systems, award statements, and reports necessary to recognize more than one PI. NIH expects to begin accepting applications with more than one PI in May 2006.

Interdisciplinary Research. To lower organizational barriers and advance science, the Roadmap initiatives launched by this working group are designed to make it easier for scientists to conduct interdisciplinary research. Among the initiatives are "no-cost" activities intended to change NIH policies and procedures in order to lower administrative barriers.

- *Interdisciplinary Research Consortia*. The Exploratory Centers for Interdisciplinary Research component of the NIH Roadmap combines disciplines to allow new ways of thinking about major problems in biomedicine that have been difficult to solve. Three of the

Exploratory Centers are focused on obesity—a prime example of a difficult biomedical problem that requires an interdisciplinary approach. Other problems being explored include stroke, cardiovascular disease, antibiotic resistance, schizophrenia, vaccine research, and pregnancy outcomes.

High-Risk Research. Many scientists who participated in the development of the NIH Roadmap advised that it would be helpful to create a new means to identify and support scientists with ideas that have the potential for high impact but that may be too novel, span too diverse a range of disciplines, or be at too early a stage to fare well in the traditional peer review process.

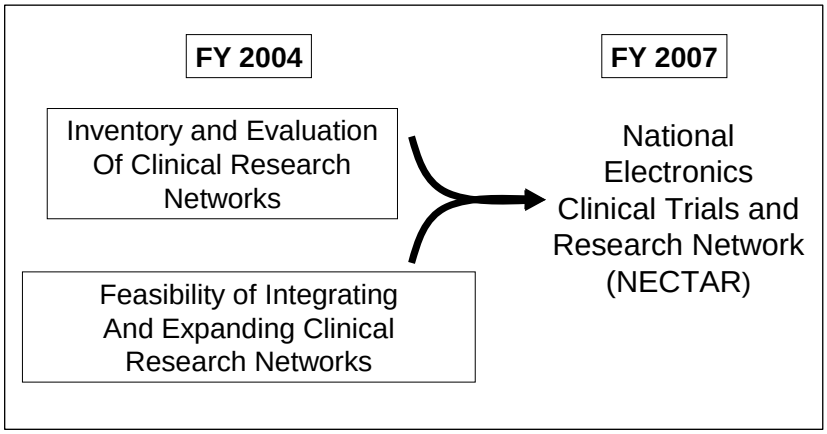
- *NIH Director's Pioneer Award*. The NIH Director's Pioneer Award is unlike other NIH research grant mechanisms in that it supports people, not projects. This innovative program will be in its fourth funding cycle in FY 2007.

Re-engineering the Clinical Research Enterprise

The NIH Roadmap initiatives for this theme are designed to incorporate modern information technology into clinical research; improve the integration of clinical research networks; stimulate the development of more effective means to assess subjective clinical outcomes; facilitate the coordination of clinical research policies; improve clinical research workforce training; and support key elements of the translational research infrastructure.

- *Dynamic Assessment of Patient-Reported Chronic Disease Outcomes.* 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 was implemented to develop and test methods of measuring patient-reported outcomes. The initiative is creating a computerized adaptive testing (CAT) system that will allow for efficient, robust, individualized, and cost-effective assessment of patient outcomes across a broad range of chronic diseases.

- *Integrating Clinical Research Networks, Enhancing Informatics, and NECTAR.* A two-phased effort is underway to integrate Clinical Research Networks: (1) an inventory and evaluation of clinical research networks is providing information on best practices in existing networks (both organizational networks and their informatics infrastructure) and (2) feasibility studies are testing concepts for enhancing the interoperability and capacity of informatic networks. Results from these studies will contribute to the development of the National Electronic



Clinical Trials and Research Network (NECTAR), an informatics infrastructure for interconnected and interoperable national research networks. NIH plans to launch NECTAR in FY 2007.

- *NIH and Public Trust:* An inventory of activities for generating public trust was compiled, from successes in individual NIH Institutes and Centers, for possible replication across the NIH. A website for the NIH Public Trust Initiative was developed (http://publictrust.nih.gov). The NIH Council of Public Representatives, in close collaboration with the Public Trust Initiative staff, held a widely attended workshop on "Public Trust in Clinical Research" and presented a report and recommendations to the Advisory Committee to the Director (http://copr.nih.gov/reports/public_trust.asp). A major community outreach effort targeting Alaska Native populations was conducted by a delegation of NIH staff to better understand the culture and to build stronger bridges for carrying out research activities. The model and lessons learned from this outreach effort are being used to tailor outreach activities with other communities. Finally, the Co-Chairs of the Public Trust Initiative are communicating broadly with many NIH "publics," including groups both internal and external to the NIH, to advance the public trust agenda.

CLINICAL AND TRANSLATIONAL SCIENCE

Today, major shifts in priorities at academic health centers, brought on in large part by changing systems of health care delivery, constrain the conduct of clinical research. For example, an exploding demand for clinical services and greatly reduced financial margins have combined to dramatically limit the time clinical scientists have to do research or to train the next generation of clinical scientists. At the same time, new trainees need to master an increasing complexity of knowledge. These challenges are limiting professional interest in the field and hampering the clinical research enterprise at a time when it should be expanding.

To meet this challenge and to capitalize on Roadmap initiatives, NIH launched the Clinical and Translational Science Award (CTSA) program in October 2005. The CTSA program aims to enable institutions to transform their own environments by creating either a center, department, or institute to promote the development and advancement of clinical and translational science as a distinct discipline. The CTSA program will assist institutions in forging a uniquely transformative, novel, and integrative academic home for Clinical and Translational Science that has the consolidated resources to (1) captivate, advance, and nurture a cadre of well-trained multi- and inter-disciplinary investigators and research teams, (2) create an incubator for innovative research tools and information technologies, and (3) synergize multi- and inter-disciplinary clinical and translational research and researchers to catalyze the application of new knowledge and techniques to clinical practice at the front lines of patient care. In addition, this innovative research "home" will provide for biomedical informatics and data management; clinical research resources, with space and personnel for inpatient, outpatient, and community studies; and cutting-edge core technologies and laboratories. The program aims to transform clinical and translational science into a new discipline by, for example, stimulating creation of promotion and tenure pathways for clinical investigators and by strengthening, integrating, and expanding clinical infrastructure resources.

These new Clinical and Translational Science entities are expected to serve as magnets that concentrate basic, translational, and clinical investigators, community clinicians, clinical practices, networks, professional societies, and industry to facilitate the development of new professional interactions, programs, and research projects. NIH anticipates that these new institutional arrangements, coupled with innovative advanced degree programs, will foster the development of a new discipline of Clinical and Translational Science that will be much broader and deeper than the classical and separate domains of translational research and clinical investigation.

This program will give research institutions more freedom to foster productive collaboration among experts in different fields, lower barriers among disciplines, and encourage creative, new approaches that will deliver better treatments to patients with complex and chronic medical diseases. Ultimately, patients will be better served because new prevention strategies and treatments will be developed, tested, and brought into medical practice more rapidly.

AGING

Currently 35 million Americans are over the age of 65. By 2030, this number will double, and comprise 20 percent of the population. Moreover, there will be explosive growth among those over 85 years of age, who are most at risk for disease and disability.

The aging of the population has important implications for our Nation's health. Almost 80 percent of people over 70 have at least one of several potentially disabling chronic conditions. Through research, NIH is working to improve the health and well-being of older Americans. The agency's portfolio emphasizes research aimed at increasing the years of active life.

Alzheimer disease (AD), the most common cause of dementia among people over 65, is one of the most serious threats to the Nation's health and economic well-being. Currently, 4.5 million Americans are affected by the disease and that number is expected to almost triple by 2050. Those suffering from AD advance inexorably, from early, mild forgetfulness to a severe loss of mental function and inability for self-care.

Research suggests that AD pathology begins to develop in the brain long before clinical symptoms yield a diagnosis. The ability to make an accurate early diagnosis of AD would allow targeted intervention before cognitive loss becomes significant. Scientists are searching for valid, easily attainable biological markers that

DHA Reduces Brain Beta Amyloid in AD Transgenic Mice. Docosahexaenoic acid (DHA), an omega-3 fatty acid, is involved in nerve cell communication in the brain. Health benefits ascribed to consumption of foods high in omega-3 suggest an association between consumption of fish and reduced risk of developing AD. In recent studies using mice genetically altered to display AD pathology, investigators found that mice on low DHA diets showed cognitive impairment and deleterious changes in brain biochemistry and structure, but AD mice receiving high DHA diets were protected from these effects. Diets high in DHA also appeared to protect against the production, accumulation, and toxicity of brain chemicals called beta amyloids, which are associated with AD pathology.

could help identify cases early in the course of disease. One promising direction in this research involves coated gold nanoparticles as bioprobes that can measure the concentration of substances that correlate with AD.

NIH also launched the Alzheimer Disease Neuroimaging Initiative. The 5-year 50-site project represents the most comprehensive effort to date to develop neuroimaging and other biomarkers for the changes associated with mild cognitive impairment and AD. The ongoing AD Genetics Initiative aims to develop the resources necessary for identifying late-onset AD risk factor genes, associated environmental factors such as physical activity and diet, and their interactions.

Parkinson disease (PD) and amyotrophic lateral sclerosis (ALS) are two other diseases of aging that are high priorities for NIH research. Parkinson disease results from the loss of dopamine-producing brain cells and usually affects people over age 50. The causes of Parkinson disease are unknown. NIH is researching the capability of adult stem cells to replace certain lost or damaged brain cells. ALS is a progressive and debilitating neurodegenerative disease, which affects people 40-70 years old. In ALS, specific neurons in the spinal cord degenerate, leading to muscle paralysis and death. Ongoing ALS research demonstrated that mice treated with a gene for a neuroprotective agent, in combination with exercise, obtained enhanced motor neuron survival, improved motor function, and prolonged lifespan. These studies add to the growing body of evidence identifying gene therapy, especially in combination with physical activity, as a promising therapeutic approach for neurodegenerative diseases.

While calcium is critical to many cellular functions of the body, the presence of calcium deposits in blood vessels indicates the development of coronary heart disease (CHD), one of the leading causes of death in the U.S. for both men and women. Recent findings suggest that measuring coronary artery calcium via electron-beam tomography, a noninvasive imaging technique, may be of value in predicting CHD-related events in individuals who do not demonstrate any signs of heart disease.

Combination Therapies for Osteoporosis. Osteoporosis, a disease in which bones become porous and subject to fracture, affects close to 10 million older people in the U.S. The condition is often silent and is frequently detected only after a fracture occurs. Osteoporosis is typically treated with either parathyroid hormone (PTH), which stimulates bone formation, or with drugs like alendronate, which slows breakdown of bone. NIH launched a study of combination therapies in osteoporosis, comparing the drugs singly, as well as in combination—the kind of study drug manufacturers are less inclined to undertake. A recent study found that a 1-year treatment with PTH, followed by a 1-year treatment with alendronate, is more effective in enhancing bone mineral density than using either of these treatments alone. It also revealed that gains in bone density achieved through PTH are lost if patients do not prevent bone breakdown by taking alendronate afterwards.

Highlights of FY 2007 initiatives include:

- *Alzheimer Disease Preclinical Drug Discovery and Development.* Expanding on former initiatives, scientists will test and develop novel compounds for their ability to slow, halt, or reverse the decline in cognitive function associated with AD, with the expectation that many of these compounds will be submitted to the U.S. Food and Drug Administration (FDA) for approval as investigational new drugs.

- *Imaging Studies Ancillary to the Osteoarthritis Initiative.* Although both x-ray and MRI are used to assess the presence and progression of osteoarthritis (OA), which is a very common disease with varying presentations, neither method has been shown to correlate with changes in clinical function or pain. This expanded initiative seeks to develop and validate novel imaging methods for monitoring the onset, and assessing the progression, of OA in order to facilitate the development of disease-modifying drugs.

- *Network for Cardiothoracic Surgical Investigations in Cardiovascular Medicine.* New surgical procedures and devices are often incorporated into clinical practice without objective evaluation of their relative benefit compared with established therapies. For example, despite the lifesaving nature of cardiac surgery, the large number of patients who undergo this surgery, and its major impact on health care resources, few cardiac surgery patients participate in clinical studies or trials. Formation of this network will enable rigorous clinical trials of new surgical techniques, technologies, devices, and bioengineered products.

- *Community-Based Rehabilitation Intervention*. In a new initiative, NIH will promote translational research projects in rehabilitation therapies. Translating rehabilitation therapies from research institutions into successful therapies in community settings is a critical priority, given pressures on the U.S. health system by the aging baby-boomer generation.

THE BRAIN

The rising public health impact of disorders of the nervous system make neuroscience one of the most important scientific frontiers for biomedical and behavioral research in this century. Discoveries in the areas of pain, alcoholism, drug abuse, autism, schizophrenia, depression, and other mental disorders are increasing dramatically. The recent creation of the NIH Neuroscience Blueprint, a new intra-agency partnership to accelerate neuroscience research, underscores the importance NIH places on ameliorating the costs and suffering associated with these complex diseases of the brain and nervous system.

Unraveling Mechanisms of Disabling Brain Disorders. Researchers focused on a genetic variant of a critical protein in the brain that is associated with risk for depression. Imaging studies revealed that individuals with the genetic variant had smaller brain regions that regulate emotion and had deficits in the circuit for processing negative emotion. These differences may increase vulnerability to depression. In studies of schizophrenia, researchers found that individuals with a variant of a gene called COMT had a reduction in an important brain chemical, dopamine, which resulted in impaired communication between the middle and front of the brain. Collectively, these imaging studies are uncovering relationships between genes and how the brain works, while providing valuable markers of vulnerability to mental disorders that allow for patient monitoring and prompt treatment.

The identification of both the genes and the parts of the brain involved in mental disorders is among the most exciting advances produced by NIH-supported researchers. Recent studies used genetics and brain imaging to investigate two of the most common, disabling brain disorders—schizophrenia and depression. The combined power of genetics and brain imaging revealed critical information about the biological basis for these diseases that may result in improved diagnostics and therapies. (See text box: "Unraveling Mechanisms of Disabling Brain Disorders.")

Researchers are working to improve imaging technologies to be able to visualize processes in the brain as they happen. Gaining an understanding of the nerve circuits underlying function in the cortex is one of the most difficult and important challenges in neuroscience. Alzheimer disease, stroke, depression, epilepsy, and schizophrenia are all disorders of cortical function and represent a significant public health burden. The increased understanding of these circuits paves the way for improved diagnosis and treatment of these common diseases and reduced burden on the Nation in terms of both suffering and health care costs.

In addition to impressive advances in neuroimaging, researchers continue to develop multiple unique approaches to study the brain. Experiments in animals allow genetic manipulations that are not possible in man but are important for developing disease models that are extremely valuable for studying brain circuitry in both health and disease and for testing new drugs.

NIH must be able respond to emerging health issues of national concern. Transmissible spongiform encephalopathies (TSEs), which include prion diseases, such as mad cow disease, are an example of such a problem. The lack of a test to rapidly detect TSEs in animals and humans has been a major barrier in detection and diagnosis. In response to this national health concern, NIH-supported researchers used a unique approach to develop a novel rapid test for prion diseases that enables diagnosis in routine monitoring of cattle for rare cases of mad cow disease. (See text box: "Detecting Prions in Blood.")

Detecting Prions in Blood. Transmissible spongiform encephalopathies (TSEs), or prion diseases, affect humans and animals. Animal forms of the disease, such as mad cow disease, can be transmitted to people. Because of the unusual nature of prions, the standard approaches to amplifying and detecting contamination in blood and other tissues do not work for TSEs. Researchers developed a significantly improved method to detect abnormal prions in blood and other tissues. The novel process allows a more than 10 million-fold amplification of the abnormal prions, allowing easy and accurate prion detection. In addition to improving the safety of the blood supply and surveillance of cattle, this sensitive TSE test is important for developing therapies, which are more likely to be effective if administered as soon as the disease is identified.

Another example of NIH-supported research directly aimed at improved health care for Americans is drug-effectiveness studies. New drugs are usually more expensive than older ones (roughly 10 times more expensive), and NIH plays a critical role in determining whether new, more expensive drugs are better than existing, less expensive medications. NIH is supporting just such an investigation in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, which is conducting clinical trials to compare the effectiveness and side effects of five medications for schizophrenia, including both new and old medications. (See text box: "Comparing Expensive New Drugs to Existing Treatments.") These and other clinical trials seek to place current knowledge of mental health treatments into a real-world context and answer real-world questions.

Comparing Expensive New Drugs to Existing Treatments. The NIH Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study compared the effectiveness of older and newer antipsychotic medications used to treat schizophrenia. Results from the first phase of the study suggest that newer, "atypical" antipsychotics are not much more effective than older, conventional antipsychotics, although all the medications studied have unique side-effect profiles. The older medication, perphenazine, was as effective as three of the four newer drugs. The fourth compound, olanzapine, was slightly better than all the others in terms of discontinuation and hospitalization rates, but was associated with higher rates of weight gain and metabolic side effects. Later phases of this study will examine issues such as switching from one treatment to another, use of health services, and cost-effectiveness.

The NIH Neuroscience Blueprint

The Neuroscience Blueprint was inspired by recognition that unifying themes in neuroscience research are fundamental to understanding the normal and disordered nervous system and to developing better prevention and treatment strategies. Three themes bear on the missions of all Blueprint Institutes and Centers: (1) neurodegeneration from disease and aging, (2) development of the nervous system throughout the lifespan, and (3) plasticity, that is, the capacity of the nervous system to change in response to the environment, experience, injury, and disease.

The Blueprint is pooling resources among 15 NIH Institutes and Centers to confront neuroscience research challenges too large for any single Institute or Center including development of research tools and infrastructure that serve the entire neuroscience community. Multi-Institute working groups focus on diseases and cross-cutting scientific issues.

Highlights of FY 2007 initiatives include:

- In 2007, the Blueprint will focus on neurodegeneration—the progressive death of nerve cells. Neurodegeneration occurs in Alzheimer and Parkinson disease, in macular degeneration and other disorders of sight and hearing, in drug and alcohol abuse, and, perhaps, in mental disorders and chronic pain. As our population ages, the impact of neurodegeneration on society will become even larger without better methods of prevention and treatment. Following the successful model of the NIH Roadmap, the Blueprint will convene scientific workshops to identify barriers to progress and exceptional opportunities and develop initiatives to provide resources, create tools, and answer key questions in neurodegeneration.

- *The Autism Phenome Project*: The project is a new activity of the Autism Coordinating Committee that seeks to identify the various clinical characteristics (phenotypes) and subtypes of autism to facilitate research on genetic and other potential causes of autism and guide individualized approaches to treatment.

- *The Human Genetics Repository:* The repository, which will be significantly expanded in FY 2007, acts as a national resource for the discovery of genes relevant to neurological disorders. Samples from patients with stroke, Parkinson disease, epilepsy, amyotrophic lateral sclerosis (ALS), and other neurological disorders are distributed to investigators in a range of research activities including clinical trials and pharmacogenetics.

- *Readjustment After Military Deployment—Risk Factors and Early Interventions to Prevent Chronic Illness and Early Death:* This new program targets the increased number of women, National Guard members, and reservists deployed in Iraq and Afghanistan to determine whether there are unique features of post-traumatic stress disorder in these groups and, if so, to test new interventions.

REGENERATIVE MEDICINE

The goal of regenerative medicine research is to develop reliable methods of replacing damaged cells, restore function, and improve health. NIH-supported researchers take varied approaches and use a broad range of cell types, in particular stem cells—adult stem cells like those found in bone marrow, umbilical cord, and other organs, and registered embryonic stem cells derived from the inner cell mass of a several-day-old embryo. All stem cells share two key traits, although to varying extents. First, they can divide repeatedly, in a process called self-renewal, producing a near-limitless supply of new stem cells. Second, when given the appropriate signals, stem cells can change or "differentiate" into the functional cells in mature tissues.

A critical aspect of regenerative medicine research is deciphering the natural signals that cue stem cells to differentiate into specific cell types such as liver, muscle, heart, bone, or neural cells. As scientists work to identify these signals, they are simultaneously learning to mimic and manipulate these signals in order to reliably change stem cells into the desired cell types that may someday repair failing heart muscles, mend a damaged spinal cord, or produce insulin in the pancreas of a type 1 diabetic.

The complement to learning what makes a stem cell change into a specific cell is learning to keep stem cells in the undifferentiated state in order to expand them into numbers large enough for experimental and therapeutic use. Therefore, an important area of study is determining the cell culture conditions to consistently grow stem cells without the cells spontaneously changing into a specific cell type such as nerve or muscle.

The Exploratory Centers for Human Embryonic Stem Cells focus on understanding the basic biology of human embryonic stem cells—what gives them the power to "self-renew" and what are the molecular signals that trigger the change from self-renewal to differentiation into mature cells. To build on findings from the Exploratory Centers, two new Centers of Excellence in Translational Human Stem Cell Research bring together stem cell experts, disease experts, and other scientists to take knowledge gained from basic research and apply it to the exploration of ways human stem cells may be used in the future to treat a wide range of diseases such as blood cancers, kidney disease, and neurological disease. The recently established NIH National Stem Cell Bank consolidates at least 11 of the federally eligible human embryonic stem cell lines in one location, reduces the cost that researchers have to pay for the cells, and maintains quality control of the growth, characterization, and distribution of the cells.

NIH-supported researchers continue to systematically investigate how both adult and embryonic stem cells work and how they might be used for lifesaving therapies. Researchers are finding stem cells in a variety of organs. (See text box: "Muscle Stem Cells Found in Mice.") Such

Muscle Stem Cells Found in Mice. NIH-supported researchers recently isolated stem cells from the muscles of mice and discovered that these stem cells can differentiate into muscle and other cell types. Importantly, the researchers worked out laboratory conditions necessary to grow the muscle-derived stem cells in numbers large enough for potential clinical applications. After transplantation into mice, the stem cells generated in the laboratory made muscle-specific proteins and maintained the form and structure of muscle cells. The researchers are now searching human muscles for similar cells, which may be useful for studying and treating human diseases due to muscle injury and degeneration, like muscular dystrophy.

adult stem cells may enable scientists to someday even engineer organs, such as muscles, kidneys, and blood vessels, which will require overcoming a number of significant challenges in building such organs from both biomaterials and cellular components. (See text box: "Engineering Blood Vessels from Human Cells.") Through basic research on stem cell biology, new discoveries are continually being made about the regulation of these complex cells.

Researchers in regenerative medicine are also looking to the body's natural healing abilities for clues as to how to re-create damaged tissues. For example, researchers found that cells circulating in the blood, not just cells in the bone marrow, are critical to repairing bone fractures. This insight may lead to the development of new strategies for promoting bone health as well as improving healing in patients whose healing response to fractures is impaired.

Engineering Blood Vessels from Human Cells. Scientists recently overcame a major barrier to producing human blood vessels in the laboratory, an important step for vascular surgery. When human blood vessel cells are cultured in the laboratory, they eventually die, preventing the generation of significant numbers of healthy cells. In part, death is caused by the fact that chromosomes become shorter when cells divide. By engineering the blood vessel cells with an enzyme called telomerase, which is capable of lengthening the end of the chromosomes, researchers increased the lifespan of the cells, which then grew into vessel-like tubes.

In other areas of regenerative medicine, the NIH is investigating the role of stem cells in aging; whether stem cells in the brain are involved in spontaneous repair following injury; and whether stem cell-based technologies can be used to regenerate organs such as the liver and kidney. A particularly promising area involves stem cell treatment for recovery from heart attack and heart failure. (See text box: "Stem Cell Repair after Heart Attack.")

Additional research areas include the development of biocompatible materials for the assembly of cells into three-dimensional structures that mimic the architecture and function of native tissue, and the prevention of tissue rejection in patients receiving transplanted cells or bioengineered organs.

Stem Cell Repair after Heart Attack. Naturally occurring stem cells, found within the damaged heart or elsewhere in the body, may play a key role in recovery from heart attack and heart failure. Investigators isolated stem cells from rats' hearts and then induced heart attacks in the rats. Stem cells reinjected into the blood stream ended up primarily in the damaged region of the heart, and developed into heart muscle and other cells essential for heart function. Importantly, the cell therapy led to the formation of new capillaries in the damaged region of the heart, and heart function was better preserved compared to that of control animals.

Highlights of FY 2007 initiatives include:

- *Enabling Technologies for Nerve Regeneration:* NIH will expand its initiative to develop novel technologies for nerve regeneration and tools to monitor nerve growth and function for the treatment of spinal cord injuries and neurodegenerative disorders.

- *Cardiovascular Cell Therapy Clinical Research Network:* This new program will accelerate development of cardiovascular disease treatments based on cell therapies by establishing a Clinical Network to conduct phase I and II cell therapy clinical protocols.

ADVANCES IN HIGH-TECH MEDICINE

The NIH aggressively supports the development of advanced technologies capable of revolutionizing health. To achieve these advances, scientists are working at the cutting edge of genomics, nanotechnology, imaging, and telemedicine. The HapMap (see the "Genes, Environment, and Health Initiative" above) is a powerful resource for studying the genetic factors contributing to variation in individual response to disease, drugs, and vaccines. The use of genomic information to determine optimal drug therapy or to determine which drugs might result in an adverse event on an individual basis is known as pharmacogenetics or pharmacogenomics. This approach, which was only an idea less than 10 years ago, is paving the way to personalized medicine, as described in the following Story of Discovery.

Story of Discovery: Pharmacogenetics Leads the Way to Personalized Medicine

The study of how genes affect how an individual reacts to a certain drug is called pharmacogenetics or pharmacogenomics. The Human Genome Project gave scientists access to the sequence of all human genes, opening up new research approaches in pharmacogenetics. The testing of patients for known pharmacogenetic variants may be one of the first clinical applications of genomics. The NIH Pharmacogenetic Research Network (PGRN) used information derived from the genome to study the molecular targets of drugs and the enzymes that remove drugs from the body. In the first 5 years of the program, PGRN researchers made nearly 400 discoveries including the following:

- **Cancer Drug Label Now Includes Pharmacogenetics Warning:** PGRN researchers found that 10 percent of the North American population have a genetic variation that puts them at high risk for life-threatening reactions to irinotecan, a drug approved in 1996 used for treating colorectal, lung, and other cancers. In the summer of 2005, the label of the drug was changed to encourage doctors to use a lower starting dose for patients known to have this variation.
- **Gene Tests Could Indicate Best Asthma Treatment:** PGRN researchers uncovered details about variations in certain genes that affect the way people respond to common asthma medications. PGRN scientists are developing gene variant tests so doctors can recommend the best treatment for each patient.
- **Sudden Death From Irregular Heartbeats:** PGRN researchers tracked down gene variants that put people at higher risk for fatal heart arrhythmias. Doctors can use this information to target high-risk patients for more aggressive screening and preventive medications.
- **Blood Thinning Done Right:** Every year in the U.S., warfarin is used to prevent blood clotting in 2 million people, including those with heart disease and those recovering from orthopedic surgery. Warfarin is tricky to prescribe, because too much causes excessive bleeding and too little could allow dangerous blood clots to form. PGRN researchers discovered that differences in a gene (VKORC1) influence the dose of warfarin that is most effective for each person, which could help doctors determine each patient's warfarin dose more quickly and precisely, without trial and error.
- **Understanding Variations in Drug Response:** PGRN researchers discovered variations in CYP3A5, a gene involved in the body's handling of more than half of all medications. Differences in this gene may help explain racial and ethnic differences in drug response, especially for medications used to treat high blood pressure.

As scientists gain a better understanding of the genes involved in different drug responses and develop tests for relevant gene variants, pharmacogenetics will steadily move from the bench to the bedside. The ultimate goal is for doctors to prescribe to all of their patients the right dose of the right medicine the first time.

The ability to apply genomic information to medicine continues to expand as novel approaches for DNA sequencing are developed. A recent breakthrough by NIH-supported scientists employs a completely new technology where thousands of chemical reactions used to sequence an individual's genome are carried out on tiny aqueous beads. With further development, the technology has the potential to decrease the cost of DNA sequencing dramatically and bring the sequencing of the DNA of individual patients for diagnosis and treatment beyond the laboratory and into the practice of medicine.

Computer and information technologies are also rapidly transforming medical practice. One of the most stunning high-tech developments involves brain computer interfaces or BCIs, which are electrical devices that assist paralyzed individuals with breathing, bowel and bladder function, hand grasping, and even standing. The most advanced BCI device detects brain waves from outside the head via electrodes on the scalp. The NIH-supported inventors and their colleagues devised ways to translate brain waves into movement of a computer cursor. With practice, people who have been otherwise unable or limited in their ability to communicate can control a computer cursor well enough to answer about four yes-or-no questions per minute. Patients who are severely paralyzed by ALS, strokes, or brain trauma may be among the first to benefit from this technology.

Beyond individual advances like BCIs, computer, information, communications, and imaging technologies are transforming the way doctors practice medicine, allowing more physicians to consult with each other and more information to be transmitted between doctors, and even allowing doctors to work on patients from remote locations. This practice, known as "Telehealth" or "Telemedicine," greatly increases the quality of care, especially for patients with complicated conditions or in remote areas as described in the Story of Discovery below.

NIH-supported researchers continue to solve complex biomedical problems with a wide range of high-tech approaches. A number of conditions that affect children are being successfully addressed with computer simulations, sophisticated electronic/biological interfaces, and improved imaging strategies. Researchers used computer-analyzed walking patterns to identify children with cerebral palsy who are likely to benefit from surgery. Continued improvements in cochlear implants help deaf children to live normal lives. (See text box: "Advances in Cochlear Implants.")

Advances in Cochlear Implants. Deaf children continue to benefit from constant improvements in the cochlear implant (CI). The CI provides stimulation directly to the auditory nerve, bypassing the damaged cochlea, which is usually the cause of deafness. A key challenge is to improve the CI user's ability to localize sound and understand speech in noisy environments. NIH-supported researchers responded with multiple technological improvements, such as CI electrodes that specifically improve hearing at high frequencies, improved sound location using bilateral cochlear implantation, and a new CI design that allows the delivery of drugs to the inner ear that can enhance auditory nerve function.

Attention deficit hyperactivity disorder (ADHD) syndrome is a brain disorder that manifests as a pattern of inattention and/or hyperactivity/ impulsivity that is more frequent and severe than is typically observed in children of the same age. ADHD begins in childhood and, as has only recently been understood, can persist into adulthood as well. A diagnosis of ADHD is currently determined on the basis of patient history and behavioral assessment. There are no other tests to definitively ascertain whether a patient

has the disease. This has led to a growing concern that current medications to treat the disease are over-prescribed. To address this problem, researchers are working on improved imaging strategies with the goal of developing a definitive diagnostic test for ADHD.

Story of Discovery: Digital Doctors and Mobile Medicine

Telehealth, which is a result of advances in communications, computer science, informatics, and medical technology, is broadly defined as the use of communications technologies to provide and support health care at a distance. Telehealth can be as simple as two doctors talking on the phone about a patient's care or as elegant as the use of robotic technology to perform surgery remotely—in another region of the country or halfway around the world.

Improving the Quality of Care Through Teleconsultation

For patients with complicated cases or chronic illnesses, especially those in rural or outlying areas, teleheath consultation with an appropriate specialist can vastly improve the quality and outcome of their health care. Often, imaging technologies like magnetic resonance imaging (MRI), computerized tomography, and ultrasound are used to diagnose or monitor a disease process, and, typically, hundreds of images are generated and transmitted to a consulting physician.

One NIH researcher developed a visual guidance system to direct rural health care providers in acquiring diagnostic medical ultrasound images. The system allows the expert to actively guide the untrained health care provider in acquiring the images. The expert provides guidance through a visual and anatomic interface that projects a schematized three-dimensional image of the target organ onto a video display. The appropriate image is projected onto the examiner's screen to serve as a visual tutorial to guide image acquisition.

Remote Monitoring: Reducing Surgical Risk

Intraoperative monitoring (IOM) is a technique that allows a surgeon to perform continuous checking, recording, and testing during a surgical procedure. The system allows localization of anatomical structures, such as peripheral nerves, which helps guide the surgeon during surgery and monitors changes in function to avoid inadvertent irreversible damage during sensitive surgical procedures. In small regional hospitals where monitoring is difficult to perform because of lack of expertise, NIH researchers developed technologies for multimedia remote IOM systems capable of transmitting data, voice, and images over the Internet. The researchers formed an interdisciplinary team—electrical engineers, neurophysiologists, and neurosurgeons—to develop new methods for improved synchronization and integration of multimedia data for remote IOM, allowing this sophisticated approach to treatment to be used in such locations.

Another NIH researcher is developing a high-resolution, three-dimensional (3D) color display for use in telehealth applications. Such a display would improve remote medical teaching, assist less skilled personnel in medical diagnosis, and further facilitate the sharing of 3D imaging data between networked sites for the purpose of improving diagnosis and treatment. Although it is technically very challenging, success in this endeavor will provide an enormous boost for future medical telehealth applications.

Personalized Medicine: Tune In for Tomorrow's Successes

The advent of miniaturized devices and wireless communication is stimulating the development of portable diagnostic and monitoring devices, which allow patient testing in the doctor's office. Combined with suitable telehealth technologies, these new devices allow physicians to make more informed and quicker decisions in their office, known as point-of-care treatment. Importantly, these advances address the challenges of health disparities by providing diagnostic capabilities to communities with limited access to large health care facilities. Multiple assays such as blood gases, electrolytes, chemistries, coagulation, hematology, glucose, and cardiac markers are done quickly and simultaneously, as samples do not have to be shipped offsite to a centralized laboratory. The NIH contributed to advances in this area by funding the development of sensor and microsystem technologies for point-of-care testing.

Nanotechnology involves the creation and use of materials and devices at the level of molecules and atoms. Research in nanotechnology began with applications outside medicine and is based on discoveries in physics and chemistry. NIH-supported researchers used an ingenious nanotechnology-based approach to move closer to a reliable method to diagnose early Alzheimer disease, which now can only be definitely determined by the examination of brain tissue after death. Using this ultrasensitive, nanoparticle-based strategy called barcode amplification to detect the small peptides, a million-fold increase in sensitivity over the previously used assay was achieved. This technique offers promise for a much-needed improved means of early AD diagnosis, which could then allow early treatment for this devastating disease.

These and other practical applications of advanced technologies illustrate the significant payoff that can come from NIH investment in this science. The advances described here promise to be only the beginning of revolutionary breakthroughs in health care through continued investment in cutting-edge technologies.

Highlights of FY 2007 initiatives include:

- *Integrated Sensors and Lab-on-a-Chip for Laboratory Tests at the Patient Point of Care:* This initiative will significantly expand the program for development of integrated microsystem and microsensor technologies capable of providing diagnostic results at the point of care.

- *Image-Guided Surgery for Minimally Invasive Treatments:* This initiative will expand NIH work on means to integrate imaging techniques with minimally invasive surgical instruments. The aim is to enable surgical procedures with fewer complications and shorter hospital stays.

- *Nanocomposite Materials for Dental Restorations:* This new initiative will support the production of a new generation of nanocomposite materials with enhanced adhesive bonding to the tooth surface, improved durability, better aesthetics, and maximum biocompatibility.

CANCER

NIH investment in cancer research is making a real difference. In the U.S., death rates from all cancers combined dropped 1.1 percent per year from 1993 to 2002. Many people who have or had cancer are living longer and enjoying a better quality of life than was possible years ago. Many people are adopting healthy habits that reduce their chances of getting certain types of cancers. For example, the smoking rate among adolescents is heading downward. Also, preventive and early detection practices have improved. Notably, screening rates for colorectal, breast, and cervical cancer are rising.

Yet cancer remains a major public health problem with more than 1 million Americans per year diagnosed with some form of cancer. Not all cancer death rates are going down. The rates of cancer of the esophagus continue to rise, as have the rates of new cases of melanoma, leukemia, non-Hodgkin lymphoma, myeloma, and cancers of the prostate, thyroid, kidney, and breast.

The burden of some types of cancer weighs more heavily on some groups than others. The rates of both new cases and deaths from cancer vary by socioeconomic status, sex, and racial and ethnic group. Also, as the Nation's population grows and ages, the number of cancer cases will increase. Therefore, despite significant progress, the cancer challenge remains formidable and the NIH investment in cancer prevention, diagnosis, and treatment is critical to the health of our citizens. NIH supports a broad range of research to both expand our understanding of cancer and develop improvements in diagnosis, prevention, and care.

A High-Resolution Map of Active Promoters in the Human Genome. NIH-supported researchers used a novel approach to search the entire genome of a cell to identify all of the regions that control whether a gene is turned on (regions known as promoters). This global approach is the first to explore the entire human genome to find all possible promoter regions. This advance provides an important tool for better understanding the molecular changes associated with cancer and for distinguishing cancer cells from non-cancer cells based on the on/off pattern of several thousand promoters.

The sequence of the human genome and related technologies is an unprecedented resource that is leading to significant new approaches to diagnosis and treatment. For example, gene expression profiling of tumor cells (identifying which genes are expressed in specific tumor types) is a method for determining the characteristics of a tumor. This information is critical for accurately diagnosing cancer and identifying the most effective treatment(s) for specific tumor types. Scientists used this approach to identify cell-specific responses to chemotherapeutic agents in breast cancer. The researchers performed a series of gene expression profiling experiments on cancer cells that originated from different types of cells found in the breast. In response to chemotherapeutic agents, different types of cancer cells turned off completely different subsets of genes. The scientists confirmed these findings in experiments using actual tumor tissue. This work is an important step toward matching the most effective drugs with specific types of tumors for an improved patient outcome.

Through the Cancer Genome Atlas project, NIH is expanding the capacity of the cancer community to exploit information on cancer genes. The Atlas, now under development, will provide a comprehensive collection and analysis of genetic mutations found in human cancers. The ongoing project includes the genome sequence, gene expression profiles, and related information on thousands of individual tumors from dozens of different tissue types. Input on the project was gathered at a 2005 workshop that included experts in cancer and clinical research, genomics, technology development, bioinformatics, and bioethics as well as the public, nonprofit, advocacy, and private sectors. In 2006, a pilot project began to address all of the technical and scientific issues in preparation for a full, large-scale project to maximize the use of genome-based information for cancer research.

A growing area of interest to cancer researchers is the reaction of the body's immune system to a developing tumor, as chronic inflammatory immune responses are known to exacerbate certain cancers. In one study, researchers looking for an improved diagnostic test for prostate cancer took advantage of the immune system response to tumor growth to develop a new, more sensitive test for prostate cancer. (See text box: "Improved Diagnosis of Early Prostate Cancer.")

Improved Diagnosis of Early Prostate Cancer. Antibodies are proteins produced by immune cells to destroy viruses, bacteria, and other foreign substances that invade the body. Scientists know that cancer patients produce antibodies against tumors. To explore the idea of using tumor antibodies to diagnosis cancer, NIH scientists devised a blood test to screen for 22 antibodies produced in men with prostate cancer. This new antibody blood test predicted the presence of cancer accurately 92 percent of the time (the currently used test, called PSA, is correct 79 percent of the time). Also, the new test has a much lower rate of false positive results than PSA. Scientists are enthusiastic that, while this study focused on prostate cancer, the general approach of antibody testing has potential to be developed for other cancers.

A major force in the development of new strategies to fight cancer is the 60 NIH Cancer Centers located across the Nation. The Centers are vital hubs of scientific activity that also develop and provide cutting-edge lifesaving prevention and treatment interventions to patients, their families, and the public. Cancer Centers extend their reach into the community through networks that link the Centers with community hospitals and private oncology practices to provide patients with state-of-the-art care and access to clinical trials. See text box*:* "Combination Therapy Improves Breast Cancer Survival.")

In early January of 2006, clinical trials performed through a network of NIH Cancer Centers identified a new treatment regimen for ovarian cancer, which accounts for approximately 4 percent of all women's cancers and is the fourth leading cause of cancer-related death in U.S. women. The new treatment, which involves the administration of high doses of chemotherapy drugs directly into the abdomen, boosted survival of women with advanced ovarian cancer by 16 months—the first significant advance in more than a decade against this highly lethal cancer in women.

Combination Therapy Improves Breast Cancer Survival. Two large clinical trials conducted by NIH Cancer Centers tested a combination therapy of trastuzumab and chemotherapy for patients with early-stage "HER-2 positive" breast cancer. Breast cancer patients are considered "HER-2 positive" if their cancer cells make too much of a protein called HER-2, which causes the tumors to grow faster and recur more often. Trastuzumab is a monoclonal antibody that inactivates the HER-2 protein. The trial was stopped and the results were made public before the clinical trials were completed because the studies showed that the addition of trastuzumab to chemotherapy significantly increased disease-free survival. Patients who received trastuzumab in combination with chemotherapy had a 52 percent decrease in disease recurrence and a significant improvement in overall survival, compared to patients treated with chemotherapy alone. For women with this type of aggressive breast cancer, the addition of trastuzumab to chemotherapy reverses the prognosis from unfavorable to good.

NIH plans to expand the geographic coverage and impact of Cancer Center services by adding up to 15 new Cancer Centers over the next 5 years, increasing the number of Centers from 60 to as many as 75. This growth will establish Centers in states and in metropolitan areas where none currently exist and improve access to care for minority and other underserved populations.

Highlights of FY 2007 initiatives include:

- *Informatics Tools to Support Clinical Trials:* To improve cost-effectiveness and comparability of results across cancer trials, NIH will substantially expand its support for a shared cancer information technology infrastructure. The goal is to create an integrated national cancer trials network.

- *Imaging for Cancer Research and Care Management:* NIH will substantially expand the development of new imaging technologies to enhance understanding of cancer biology, facilitate the preemption and clinical management of cancer and cancer risk, and advance imaging options important to other diseases as well.

- *Computational Modeling to Support Research and Patient Care:* This initiative will substantially expand support for interdisciplinary collaboration among computer scientists, physicists, and cancer scientists to create computational models for computerized prediction of cancer outcomes, including patient response to treatment.

OBESITY AND DIABETES

Today, almost 65 percent of U.S. adults aged 20 years and over are overweight, and about half meet the criteria for obesity. This is an epidemic and it is worsening. Recent studies suggest that, over the next few decades, life expectancy for many Americans could decline by as much as 5 years unless aggressive efforts are made to slow rising rates of obesity. Perhaps more alarming, the epidemic is not restricted to adults. The percentage of young people, aged 6 to 19 years, who are overweight has more than tripled since 1980; 16 percent are now considered overweight. Infant and childhood obesity is predictive of adult obesity.

The public health implications of these trends are deeply troubling, as the list of diseases and health conditions associated with obesity includes hypertension, coronary heart disease, stroke, gallbladder disease, osteoarthritis, sleep apnea, respiratory problems, and some cancers. One of the more profound risks associated with obesity is type 2 diabetes, which in turn is associated with serious and life-threatening health problems including a greater risk of heart attack, stroke, blindness, and kidney failure leading to nerve damage, severe pain, and limb amputation, disability, and even early death.

"We Can!" Promotes Healthy Weight Maintenance. A 3-year NIH study of preadolescent children found that behaviorally oriented nutrition education was effective in changing dietary habits. Based on the study, a group of NIH Institutes collaborated on the design and launching of "We Can!" a national program providing a one-stop resource for parents and caregivers interested in practical tools to help children 8-13 years old stay at a healthy weight. Three critical behaviors are stressed: improved food choices, increased physical activity, and reduced time being sedentary.

The problem of overweight and obesity is multifactoral and deeply rooted in modern life. The importance and complexity of the obesity epidemic requires a coordinated and accelerated response from Federal agencies. To this end, NIH co-chairs a White House interagency work group on nutrition, physical activity, and obesity.

Here at NIH, the NIH Obesity Research Task Force has been active for over 2 years and in that short time developed and moved forward to implement a dynamic strategic plan (http://www.obesityresearch.nih.gov/about/strategic-plan.htm). NIH is funding a broad spectrum of obesity-related research that aims to increase understanding in three areas, as discussed below.

1. Preventing and treating obesity through behavioral and environmental approaches to modify lifestyle.

2. Preventing and treating obesity through pharmacologic, surgical, and other medical approaches.

3. Breaking the link between obesity and associated diseases, such as type 2 diabetes, heart disease, and cancer.

Lifestyle Modification

Ongoing research is testing the effectiveness of behavioral interventions that promote the adoption of healthy lifestyles. A key area of concentration is long-term weight maintenance. NIH is investigating a number of factors, including behavioral and psychological, relevant to weight regain. Another special focus of obesity research is the development and testing of culturally appropriate interventions, such as those designed specifically for American Indian and Alaska Native populations. Other ongoing research addresses school-based interventions. Weight loss is more readily maintained if achieved prior to puberty. Carrying out research on behavioral interventions often requires measuring calorie intake and energy expenditure. However, this is remarkably difficult to achieve and the inconvenience, expense, and relative inaccuracy of current methods are a serious barrier to progress. Research on novel sensors and other devices to accurately measure calorie intake and energy expenditure will be of great benefit. Even sleep presents a target for intervention. Several studies have found a correlation between sleeping less than 8 hours per night and an increase in body mass index.

Medical Interventions

NIH investigates pharmacologic, surgical, and other medical means to prevent and treat obesity. We know from previously supported NIH research that an elaborate network of brain, gut, and cell-derived hormones control appetite, energy expenditure, and the integrated regulation of metabolism by many organs in the body. This knowledge provides opportunities for drug development that is advancing on many fronts (e.g., see text box "Alcohol Researchers Find Fat-Promoting Receptor in Liver Cells."). In addition, understanding the genetic basis of obesity will enable scientists to develop more targeted prevention efforts and novel therapies. Around 50 to 70 percent of the variation in body weight is genetically determined, according to NIH-supported research.

Understanding how factors other than diet and exercise influence obesity is essential to addressing this national problem. For example, a recent NIH study documented that the presence of certain microorganisms in the digestive tract has a role in obesity.

Alcohol Researchers Find Fat-Promoting Receptor in Liver Cells. Scientists already knew that a receptor, called CB1, has a role in obesity because it stimulates appetite when activated by naturally occurring chemicals. Now, alcohol researchers discovered that CB1 is present in the liver, where, when activated, it directly stimulates fat production. Already, a weight-loss drug that inhibits the CB1 receptor is being developed by a French company.

Breaking the Link between Obesity and Associated Diseases

As we understand the basis for the links between obesity and associated diseases, we will find targets for intervention—steps in the disease process where we can break those links. Research is looking at where fat is deposited and how fat in one location differs from fat in another. Although fat in the abdominal cavity appears to be more highly associated with secondary disease than fat under the skin, the basis for this association is not clear.

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

Genetics presents another front on which to fight the downstream impacts of obesity. In a recent finding, researchers discovered mutations in a gene that suggest a genetic mechanism for the link between childhood obesity and the high risk of type 2 diabetes in adolescence and adulthood. These findings present new opportunities for strategies to prevent and treat obesity and diabetes.

Highlights of FY 2007 initiatives in obesity include:

- *Collaborative Research between Basic and Clinical Researchers in Obesity*. Because obesity is a particularly multifaceted health issue, the development of close collaborations between basic and clinical researchers holds particular promise for the advancement of knowledge. In FY 2007, NIH will significantly expand an initiative that promotes such collaboration so that basic and clinical researchers in obesity can benefit from methodologies and techniques in each other's domains.

Diabetes

Diabetes is not just the consequence of obesity. Many people who are not obese suffer from this devastating disease. Nearly 21 million people in the U.S.—7 percent of the population—have diabetes, the most common cause of blindness, kidney failure, and amputations in adults and a major cause of heart disease and stroke. At least 65 percent of people with diabetes will die from a heart attack or stroke.

Linking Genes to Type 2 Diabetes. Recent research by a team of scientists from NIH and around the world identified variants in a gene that may predispose people to type 2 diabetes. The researchers identified four genetic variants that are strongly associated with type 2 diabetes. 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. Knowing the errant genes provides new targets for both prevention and treatment of this disease.

This year research yielded information that could have a profound effect on the lives of diabetics. Researchers found that if patients with type 1 diabetes maintain a tight control over their glucose levels, they can lower their risk of heart disease and stroke by about 50 percent. This finding builds on earlier results of the Diabetes Control and Complications Trial (DCCT) that clearly showed that intensive glucose control

prevents or delays the eye, nerve, and kidney complications of type 1 diabetes. The DCCT findings prompted a major shift in the way doctors manage their patients with type 1 diabetes. As researchers continued to follow participants, they saw that intensive treatment reduced the development of atherosclerosis, a finding published in 2003. They also observed a striking advantage of intensive control–its long-lasting effects on heart attack and stroke. Mounting evidence suggests that tight glucose control benefits everyone with diabetes. Researchers expect a definitive answer on the benefits for people with type 2 diabetes from the ongoing ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, a major study testing ways to lower the risk of heart disease and stroke in adults with type 2 diabetes.

Treatment for Blood Sugar Maintenance in Type 2 Diabetics. NIH research revealed that sugar in the stomach provides a key to insulin release. This finding and subsequent research resulted in development of a drug, "exenatide," which mimics the effects of food in the digestive system, causing diabetics to maintain healthy glucose levels and also lose weight. In April 2005, the Food and Drug Administration approved exenatide as a supplementary treatment for type 2 diabetes in patients with difficult-to-control blood sugar. Scientists are eager to explore potential benefits of exenatide in treating or preventing type 1 diabetes.

Genetics is another important front in diabetes research. The tools of genomics are beginning to reveal many details about diabetes and other common diseases that may suggest avenues for preventive interventions and treatments. Recent findings provide insights into both genetic variation and gene function.

Although maintaining tight control of blood sugar is critical for reducing organ damage in diabetics, it is not easily accomplished. Intensive, complex research in this area continues to yield treatment options for diabetics. (See text box: "Treatment for Blood Sugar Maintenance in Type 2 Diabetics.")

INFECTIOUS DISEASE

Infectious diseases are the third leading cause of death in the U.S. and the second most frequent cause of death worldwide, where infectious diseases are more prevalent. Moreover, across the globe, infectious diseases cause approximately two-thirds of deaths among children younger than 5 years, a tragedy in terms of years of healthy life lost. Infectious diseases also seriously undermine economic development, especially in developing countries, where they are both a cause and a consequence of poverty and can lead to serious political instability.

A primary challenge in infectious disease research is that pathogens have the pernicious ability to mutate into new forms that can jump species, adapt to new environments, and evade available preventives and treatments. We also know that, in the wrong hands, infectious diseases can be tools of terror. Thus, NIH addresses most infectious disease on two fronts–devising better interventions for the threats we know now and are yet to subdue and being as prepared as possible to respond to the currently unknown threats that will emerge in the days and years ahead.

Pandemic and Seasonal Influenza

NIH is working intensely against influenza. The centerpiece of this work is the development of multiple vaccines against influenza virus, including research into new approaches to vaccine manufacture and delivery. (See Story of Discovery: "Development of a Vaccine for Pandemic Influenza.")

At the most basic level of research, NIH is collaborating with numerous public and private partners on an influenza genome sequencing project, launched in 2004. The project will determine the complete genetic sequences of thousands of influenza virus strains, providing the scientific community with data vital to development of new vaccines, therapies, and diagnostics. NIH also is using sophisticated computer modeling techniques to simulate the possible courses an epidemic might take. The models are valuable tools for forecasting the best strategies to contain an epidemic. Two different models both suggest that a carefully chosen combination of public health measures along with the quick implementation and large-scale use of antiviral drugs could stop the spread of an avian flu outbreak at its source. In addition, NIH works closely with DHHS to implement the recently issued National Pandemic Influenza Preparedness Plan.

Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS)

Although we have made enormous scientific progress since HIV was first identified as the cause of AIDS, the epidemic continues to spread. Currently, more than 40 million people globally are living with HIV, with approximately 14,000 people newly infected every day.

Developing a vaccine that protects against HIV infection is one of the highest priorities of the NIH HIV/AIDS research program. The scientific challenges that must be solved to develop an effective vaccine against HIV are daunting. The fact that there has never been a documented case in which a person with established HIV infection has completely eliminated the virus underscores the magnitude of the challenge that scientists face. Thus, a successful vaccine must do better than natural infection. NIH scientists have developed a one-two punch vaccination strategy approach, consisting of an initial (prime) vaccination followed by a later (boost) vaccination. The strategy employs the three HIV strains that cause about 85 percent of all HIV infections around the world. Early clinical trials of the two vaccines indicate that they are well-tolerated and elicit measurable immune responses. A recently launched trio of phase I and II trials is being conducted by three international networks to test the safety and immunogenicity of the prime-boost strategy in the Americas, South Africa, and East Africa.

Expanding HIV Screening Is Cost-Effective. Nearly one-third of the people living with HIV/AIDS in the U.S. do not know it. Late diagnosis leads to poorer health outcomes and increases the chance of unwittingly spreading the virus. Two NIH-supported research teams independently determined that HIV screening and testing is a cost-effective means of increasing the length and quality of people's lives, even in countries, like the U.S., where HIV prevalence is relatively low. Using computer models, one team showed that HIV screening and testing compare favorably (in terms of costs per quality-adjusted life year) as screening for breast cancer and high blood pressure.

Story of Discovery: Vaccines for Pandemic Influenza

In 1918 and 1919, a new influenza strain sparked a global pandemic that killed more than 500,000 people in the United States and more than 40 million people worldwide; milder pandemics occurred in 1957 and 1968. Researchers and public health officials are now concerned that another pandemic may be on the horizon. The H5N1 influenza strain that first appeared in Hong Kong in 1997 has now spread to at least 17 countries, killed millions of birds, infected more than 150 people, and caused at least 78 deaths. If the virus develops the ability to easily transmit from human to human, it would likely spread rapidly around the globe, with potentially devastating consequences.

To prepare for a possible H5N1 pandemic, NIAID has begun testing of vaccines based on inactivated H5N1 viruses, and supports many research projects to develop new influenza vaccine candidates and new technologies to enable rapid, large-scale production of influenza vaccines.

Pandemic Vaccine Candidates. Influenza viruses are named for two of their surface proteins. The hemagglutinin protein (HA) allows the virus to bind to a cell and initiate infection, and the neuraminidase protein (NA) allows newly formed viruses to exit the host cell and infect other cells. Using a technique called reverse genetics, NIAID-funded scientists created new seed viruses that contain the H5 and N1 surface proteins. Two pharmaceutical companies used these viruses to manufacture pilot lots of several thousand vaccine doses, one of which has been clinically tested in healthy adults in NIAID's Vaccine and Treatment Evaluation Units. Results indicate that the vaccine is safe and stimulates an immune response that is predicted to be protective, although two large doses of viral antigen were required for an adequate response. Trials of this vaccine will be expanded to include testing in the elderly and children, two populations often most vulnerable to seasonal influenza. Trials with H5N1 vaccine candidates containing adjuvants—substances that increase the immune response—will begin in early 2006.

New Influenza Vaccine Strategies. Although the current influenza vaccine effectively prevents seasonal influenza, it has some limitations. Influenza viruses mutate rapidly, allowing their surface proteins to change so much between influenza seasons that prior immunization may not offer adequate protection against newly circulating strains. Thus, in order to maintain immunity people must be vaccinated annually with a new vaccine matched to the strains that are expected to circulate in the coming season. To overcome this problem, NIAID-supported scientists are creating vaccines that target viral proteins that change less rapidly than HA and NA. Vaccines based on these more stable proteins might provide protection against many flu strains simultaneously, including potential pandemic strains. The broader protection would likely result in an influenza vaccine that would be effective for multiple seasons.

The current methods used to produce influenza vaccines, while reliable, also have limitations. The complex logistics and the six-month lead time needed to grow vaccine in eggs make it impossible to boost the vaccine supply quickly in an emergency. NIAID-supported scientists are working to develop new vaccine production technologies to solve these problems. For example, NIAID has awarded multiple contracts to develop methods to grow the virus in mammalian cells cultured in large vessels. Because cell culture vessels are relatively easy to set up, manufacturing capacity could be rapidly expanded. Other vaccine production strategies that do not require growing whole virus are also under development. These include a recombinant protein vaccine, in which HA and NA antigens are grown in insect cell cultures, and DNA vaccines, in which only DNA encoding influenza proteins is injected into the recipient. Host cells then use the DNA to produce fragments of influenza proteins to which the immune system reacts.

NIAID-supported researchers are also developing better ways to deliver influenza vaccines. Beginning in the mid-1970s, NIAID investigators played a key role in the development of FluMist®, a live influenza vaccine delivered as a nasal spray. Today, NIAID intramural researchers are working with the FluMist® manufacturer to produce and test similar vaccine candidates against all influenza strains with pandemic potential, with the goal of creating capacity to rapidly produce nasal spray vaccines against pandemic strains. In addition, because vaccine supplies will almost certainly be tightly limited in the early phases of a pandemic, NIAID supports development of techniques that can increase the number of people protected by a given amount of traditional influenza vaccine. These include injecting the vaccine into skin instead of directly into muscle—a method widely used decades ago but recently neglected—as well as the potential use of adjuvants to help smaller amounts of vaccine stimulate an adequate immune response .

Even when a widely effective HIV vaccine is available, control of the AIDS pandemic will likely require a combination of prevention strategies. One prevention strategy under investigation includes topical microbicides—gels that can block HIV transmission associated with sexual activity. In the past year, there were several important advances in topical microbicide research. A large, multisite clinical trial to test the safety and preliminary effectiveness of two candidate topical microbicides (PRO 2000 and BufferGel) began in early 2005. Also, the first combination microbicide was evaluated for safety in monkeys. This is significant because combining microbicides that work against two or more different viral targets could result in a highly effective product.

Getting the Word Out About the Link Between Drug Abuse and AIDS. NIH recently unveiled a new public awareness campaign called "Drug Abuse and HIV: Learn the Link." Using public service announcements, websites, and other methods of outreach, NIH is helping people understand how injection drug use increases the risk of infection with HIV, and how other forms of drug abuse can interfere with common treatments for AIDS. The campaign, based on the latest research about the association between drug use and AIDS, is aimed at teens, who often feel invulnerable to diseases, and other high-risk groups

Severe Acute Respiratory Syndrome (SARS)

SARS is a prime example of an emerging infectious disease. First reported in southern China in the winter of 2002-2003, SARS spread to more than two dozen countries in North America, South America, Europe, and Asia before the outbreak was contained. According to the World Health Organization, a total of 8,098 people worldwide became sick with SARS during the 2003 outbreak and 774 people died. Harnessing modern molecular genetics, NIH scientists developed three distinct SARS vaccines, all of which offered protection in animals. One of those candidates, developed at the NIH Vaccine Research Center, is now being tested in a clinical trial. The first human trial opened just 21 months after SARS was recognized as a new infectious disease, reflecting the urgency with which this new threat was addressed. Three SARS vaccines produced under NIH contract will be tested in clinical trials during 2006.

Bats Harbor the SARS Virus. Understanding where the SARS virus comes from and how it begins infecting people will be key to preventing similar outbreaks in the future. Early studies indicated that the SARS virus was first passed to humans by a raccoon-like mammal called the palm civet, which is sold live in markets in China. NIH-funded researchers from China, Australia, and the U.S. have used DNA sequencing and genomic analysis and concluded that the natural reservoir for SARS virus is actually the Chinese horseshoe bat instead. This is important because although the palm civet may be important in transmitting the disease to humans, surveillance and control efforts should now be targeted to bat populations as well.

Basic Research and Other Infectious Disease Research

NIH's ability to mount such a fast and constructive response to SARS, and its future ability to intervene in the course of infectious disease, depends on the depth and breadth of our knowledge of how microbes spread and are harbored in the environment and how they cause disease. Each gain in fundamental understanding provides another handle for developing strategies to prevent, diagnose, and treat diseases caused by pathogens.

NIH also is making steady progress across a wide range of other significant infectious diseases. For example, based on an earlier discovery that antibodies found in the blood of people infected with West Nile virus (WNV) could be used to treat WNV infection in mice, NIH-supported researchers found success with a particularly effective monoclonal antibody derived from mice and engineered it into a human antibody frame. This new "humanized" WNV antibody has great potential as a treatment of people infected with deadly WNV. By using comparative genome sequencing, a team of intramural NIH scientists discovered how a promising drug candidate attacks the bacterium that causes tuberculosis. With this information, they expect to be able to optimize the drug candidate, which holds promise for shortening and simplifying the now cumbersome treatment regimen for TB. Also, NIH-supported scientists, collaborating with the Department of Veterans Affairs and Merck & Co., obtained very promising results in a test of an experimental vaccine for herpes zoster, also know as shingles. The experimental vaccine reduced the incidence of shingles by half and dramatically lessened the severity and complications of the disease in those subjects who did experience outbreaks. The test was one of the largest adult vaccine trials ever conducted.

Human Papillomavirus (HPV) Vaccine Reduces Infection and Related Disease. HPV infection causes virtually all cases of cervical cancer, the second most common cause of death from cancer in women. An investigational vaccine directed against four types of HPV, including the two responsible for 70 percent of all cervical cancers, reduced their incidence and any HPV-related disease by 90 percent. Several phase III trials testing the ability of the vaccine to protect against cervical cancer are underway. It is estimated that the successful completion of these trials and subsequent clinical dissemination of the vaccine could translate into preventing over 200,000 deaths per year worldwide from cervical cancer.

Biodefense and Infectious Diseases

The intentional release of anthrax in 2001 underscored the seriousness of the threat of bioterrorism. In addition to anthrax, the agents of most concern are smallpox, plague, tularemia, haemorrhagic viruses, and botulinum toxin. These threats are highly lethal and have the potential to be deployed as bioweapons. NIH is supporting the early and advanced development of vaccines against all these agents.

Newly Developed Monoclonal Antibodies Can Neutralize Anthrax Toxin. Inhaled anthrax spores can lodge and grow in the lungs and produce a deadly toxin. Even if all the anthrax bacteria are killed through treatment with an antibiotic, the residual anthrax toxin can still be harmful or fatal. NIH scientists have produced a monoclonal antibody that prevents this damage.

NIH also is actively researching therapeutics. Therapeutics research includes screening already-licensed drugs for activity against possible agents of bioterror. For example, NIH-supported scientists found that mice given a new cancer drug, Gleevec, can survive a lethal dose of vaccinia virus, a relative of smallpox virus. The investigators are optimistic that Gleevec or similar drugs might be used to treat smallpox infection in individuals with compromised immune systems, who are not eligible to receive the currently licensed vaccinia virus-based smallpox vaccine. Therapeutics research also includes discovery and development of new, novel interventions. (See text box: "Newly Developed Monoclonal Antibodies Can Neutralize Anthrax Toxin.")

In order to expedite the development of medical countermeasures, NIH is working in close collaboration with industry and academia. The mechanisms established by the BioShield

legislation of 2004 facilitate this interaction. NIH also is bolstering intellectual and physical infrastructure for biodefense research. In 2005, NIH completed the national network of Regional Centers of Excellence (RCE) for Biodefense and Emerging Infectious Diseases Research and continued to fund construction at biosafety facilities.

Finally, this June, NIH published a *Strategic Plan and Research Agenda for Medical Countermeasures Against Radiological and Nuclear Threats*. In turning its attention to these aspects of biodefense, NIH is working to develop therapeutics to treat and mitigate the short-term and long-term effects of radiation exposure, as well as products that can measure radiation exposure. NIH is working closely with the Armed Forces Radiobiology Research Institute on these efforts.

Highlights of FY 2007 initiatives include:

- *Services for Preclinical Development of Therapeutic Agents—Influenza Drug Screening:* Having multiple alternative interventions to treat and prevent emergent influenza strains is essential. This initiative will expand the services for preclinical drug development by facilitating the selection of the best compounds with the potential to be effective against a broad spectrum of influenza strains, including newly emergent strains.

- *Partnerships for Influenza Therapeutics and Diagnostics:* This new initiative supports the development of next-generation diagnostics and antiviral agents for H5N1 and other strains of influenza. Approaches to increase the sensitivity of existing diagnostics and the development of new technologies will be supported under the program. Activities will range from identification of new drug candidates to preclinical drug evaluation in animal models.

- *Ecology of Infectious Diseases:* Expanding on a highly successful global effort, the program seeks to understand the ecology of infectious diseases. This area represents an important knowledge gap that can only be addressed successfully through collaborative research among ecological, biomedical, and behavioral scientists. The expansion will foster more translational research to develop public health interventions based on research findings.

- *AIDS Structural Biology Program:* This new initiative will establish two to three research centers to determine the structures of complexes of HIV proteins and cellular components, which will be used as targets for the development of new anti-AIDs drugs.

HEALTH DISPARITIES

Despite tremendous medical advances and improvements in public health in recent decades, African Americans, Hispanic/Latino Americans, American Indians, Alaska Natives, Asians, Native Hawaiians and Pacific Islanders, and other medically underserved communities continue to suffer an unequal burden of illness, premature death, and disability in the U.S.

Under the umbrella of the NIH Strategic Plan to Reduce Health Disparities, research is ongoing into the biological, social, and environmental basis for health disparities, coupled with activities to foster health awareness among all populations, and efforts to increase the number of minority scientists in biomedical research. To encourage early detection, health promotion, and prevention, NIH supports a broad range of national health awareness programs. These include programs targeting African Americans and Hispanic Americans to close the health gap such as "*Take a Loved One for a Checkup Day*" and "*Celebra La Vida Con Salud*." Recognizing the urgency of the type 2 diabetes epidemic, which poses greater risks for minority groups, NIH and the Centers for Disease Control and Prevention (CDC) collaborated to develop and launch "*Small Steps. Big Rewards. Prevent Type 2 Diabetes,*" as well as a communication campaign tailored specifically for American Indians and Alaska Natives: "*Take Care of Your Heart: Manage Diabetes for Future Generations*."

Invite Them and They Will Come. A commonly accepted stereotype is that racial and ethnic minorities are less willing to participate in health research than members of the majority population. Recent findings, however, counter this widely held notion. When minorities are given the opportunity to participate in health research studies, they do so at the same rate as non-Hispanic whites. The main barrier to participation is access.

Tailored Medicine for the Heart. NIH-supported scientists helped demonstrate the efficacy of a new medication (BiDil) for African Americans with heart failure—the first time a drug has been approved for a particular racial group. The prevalence of heart failure and the premature death rate from heart disease are high among African Americans compared to other racial groups. Although all people are nearly genetically identical, a related ongoing study is investigating the subtle genetic differences amongst racial groups that might enhance patient outcomes and improve quality of life in individual responses to drugs like BiDil. Such studies should ultimately reduce disparities by identifying the most effective treatments targeted to specific populations. They also accent why it is so important to include minorities in clinical trials.

Deaths from the over 700,000 strokes that occur annually in the U.S. are roughly 40 percent greater among African Americans than among Caucasians. NIH's Stroke Prevention/ Intervention Research Program seeks to decrease incidence of stroke in medically underserved populations and to establish prevention, intervention, and rehabilitation programs. NIH also participates in the DHHS Stroke Belt Elimination initiative, which heightens awareness and seeks to improve intervention to reduce high blood pressure, cigarette smoking, and obesity—all significant risk factors for stroke in poor and ethnic minority populations. NIH offers free information in Spanish to the Hispanic community about "*accidente cerebrovascular*," providing clear information about treatments that can greatly reduce the damage caused by a stroke, and emphasizing the need to seek treatment immediately. Printed materials stress the importance of making lifestyle changes, such as smoking cessation, eating a healthful diet, exercising regularly, controlling high blood pressure, and managing diabetes.

Sickle cell disease (SCD) continues to be a significant cause of mortality, morbidity, and health disparity in the U.S. and globally. In the U.S., approximately 80,000 people, mostly African Americans, are affected. Based on the outcome of an NIH conference, a trans-NIH staff working group was formed, and a Sickle Cell Disease Clinical Research Network was initiated to create the infrastructure needed to translate results from basic and phase I/II studies into phase III trials for interventions to treat and prevent SCD and its complications. NIH also developed a

consultative Network for Sickle Cell Disease to share information with practitioners, given that mal-distribution of specialists represents a primary reason for poor availability of good care. NIH hosts an annual international Sickle Cell Disease Clinical Research Meeting.

Visual Problems Go Unseen. 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 U.S. Almost a quarter of the LALES population had diabetes—a rate twice that of Caucasians—and half of 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, and 75 percent of the Latinos were undiagnosed before the study. In addition, about 10 percent had early signs of age-related macular degeneration, and one in five adult Latinos had a cataract. These data are critical to ensuring that public health professionals target at-risk populations for screening and treatment.

Research and Training Centers Focused on Health Disparities

NIH is committed to developing and sustaining a multidisciplinary and highly diverse national biomedical research network to optimize research, training, research capacity building, and community outreach to advance scientific discovery and ensure that health disparities are reduced and ultimately eliminated. The "Research Centers in Minority Institutions (RCMI) Program" supports institutions that grant doctoral degrees in health-related fields and have a 50 percent or greater enrollment of students from minority communities. RCMI supports research that targets disorders which disproportionately affect minority populations, such as chronic kidney disease, HIV/AIDS and hepatitis C virus infection.

Because racial and ethnic minorities are underrepresented among biomedical investigators, NIH sustains a number of ongoing efforts to address this problem, aimed at ensuring an adequate cadre of future minority researchers by both supporting current investigators and encouraging junior scientists and students to pursue research careers. In addition to fellowship programs designed to help minority investigators achieve career success, initiatives such as the Research Endowment Program build research and training capacity in institutions that invest in the education and training of underrepresented minority and socioeconomically disadvantaged individuals.

Highlights of FY 2007 initiatives include:

- *Linking Related Programs to Maximize Benefit.* NIH will explore linkages between the research capacity and the research training strengths of its Research Endowment Program and its Project EXPORT Centers of Excellence. The aim of such linkage is to broaden the base of eligible institutions committed to the education, training, and improvement of the health status of ethnic and minority populations.

- *Institutional Mentors*. The ongoing Biomedical Scholars Program will recruit preeminent leaders in biomedical, behavioral, epidemiologic, health services, and translational research and other disciplines committed to the study of health disparities research and educational administration to serve as mentors to institutions committed to reducing and eliminating health disparities through research.

These and other collective efforts should develop the knowledge base to ensure that all Americans have an equal opportunity for living full, healthy, and productive lives.

MANAGEMENT INNOVATIONS

NIH actively innovates in management as well as in science and a few examples planned and recent management improvements are cited below. NIH is proud of its track record for good management as reflected in recent scores as measured by the OMB Program Assessment Rating Tool (PART). In the FY 2007 PART, the Buildings and Facilities Program and the Intramural Research Program were both deemed *Effective, with scores of 96 percent and 90 percent, respectively*. On the FY 2006 PART, the NIH Extramural Research Program achieved a similarly high 89 percent. These high scores demonstrate exemplary management and ample progress toward meeting NIH performance measures. To date, approximately 90 percent of NIH's budget has been PARTed and rated *Effective*. Specific information about the results of the PART reviews is provided in the Performance Budget Overview.

Office of Portfolio Analysis and Strategic Initiatives

With the growth and increasing complexity of the agency, NIH moved aggressively to transform its management strategies and decision-making processes. To streamline, harmonize, and better coordinate decisions that affect the entire agency, in 2003, the NIH Director established the NIH Steering Committee, composed of nine Institute Directors who serve on a rotating basis. Six working groups support the Steering Committee.

More recently, NIH addressed the need for more robust means to oversee the vast NIH research portfolio and plan and launch trans-NIH initiatives. While the NIH successfully developed important trans-NIH initiatives such as the Roadmap for Medical Research, the Strategic Plan for Obesity Research, and the Neuroscience Blueprint, the agency needs more transparent processes and cutting-edge tools to analyze, assess, and manage the array of research it supports, and provide better information to support planning and priority-setting in areas of shared Institute and Center interest. To achieve these goals, in FY 2005 NIH established a new office within the Office of the Director—the Office of Portfolio Analysis and Strategic Initiatives (OPASI). The OPASI comprises three divisions, focused on (1) resource development and analysis (including the development and deployment of knowledge management systems), (2) strategic coordination, and (3) evaluation and systematic assessments.

Collectively, the three divisions identify and integrate information to support the planning and implementation of trans-NIH initiatives that address exceptional scientific opportunities and emerging public health needs. More specifically, OPASI is facilitating a "functional integration" of strategic planning and evaluation activities across the agency, and undertaking the following key tasks:

- provide needed systems and tools to facilitate the planning and monitoring of trans-NIH initiatives, including improved methods for collecting IC data on expenditures on various diseases, conditions, and research fields, and improvements in data related to burden of disease;

- better integrate such information into agency-wide strategic plans and in setting research priorities;

- develop, with input from the ICs, common processes and formats, where necessary, for the conduct of NIH-wide planning and evaluation;

- implement trans-NIH planning efforts that incorporate broad public input—including input from scientists, health care providers, policymakers, and patient advocates—in addition to soliciting advice from within NIH;

- facilitate the coordination and implementation of trans-NIH initiatives that have been selected for support; and

- strengthen NIH-wide evaluation processes.

Through these efforts, the NIH Director and the IC Directors will have access to more consistent information to improve coordination and facilitate collaboration across the agency, and to inform priority-setting and budget decisions.

Streamlining Management Functions

In support of the President's Management Agenda (PMA) and the DHHS Secretary's goal for restructuring and consolidating administrative services, an NIH Administrative Restructuring Advisory Committee (ARAC) was established to identify opportunities for streamlining the NIH management structure in eight administrative areas. The efforts resulted in the consolidation of organizations and streamlining processes for EEO, Human Resources, Budget, Information Technology, Facilities, and Grants. Human Resources will refine processes and operations this fiscal year, to adjust to earlier consolidations. These consolidations and process improvements are in line with the implementation of complementary technological advancements, such as the NIH Business System (NBS) and the NIH Portal, which offer new means for Internet access to a broad array of resources, services, and information for NIH staff. In addition to enhanced efficiency within each administrative area, NIH is improving customer service for each consolidated area through the use of service level agreements and performance indicators. Additionally, NIH has been a supporter of the DHHS strategic sourcing initiative by recognizing the benefits of leveraged buying—increasing efficiency by reducing the number of vendors that provide similar products and streamlining the acquisition process to achieve significant savings.

Competitive Sourcing Program Achievements

Competitive sourcing, a key feature of the PMA, calls for Federal agencies to review their business functions to determine those that might be conducted more efficiently via contracts with

non-Federal businesses. During FY 2005, NIH successfully completed and won 12 competitive sourcing reviews (meaning those areas were being performed as efficiently as the private sector might perform them). Two other studies announced in 2005 are scheduled to be completed in early 2006. NIH has tentatively identified 8 additional functional areas for review in 2006 and 10 in FY 2007. The FY 2007 plan currently includes a variety of administrative support activities, the specific makeup and distribution of which will be clarified during the pre-planning phase.

Strategic Human Capital Management

NIH is completing a Workforce Planning Initiative, which will characterize the future NIH workforce for 27 institutes with varying missions and needs and guide human capital policy for the future management of NIH's complex, cutting-edge research missions. NIH will address human capital management issues, such as recruiting for chronic shortage areas, introducing new occupations, retaining the best scientists and employees, retooling the career development programs that provide opportunities for all employees, and developing a succession plan where needed. Additional improvements will occur with the implementation of systems to help facilitate the search for new talent, reduce hiring time for key positions, and integrate technology to allow the seamless transfer/sharing of information.

Implementation of Unified Financial Management System

The Unified Financial Management System (UFMS) is being implemented to replace five legacy accounting systems currently used across the Department, thereby reducing the cost of providing accounting services to the Department's organizations. Similarly, it is hoped that 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.

The NIH Business System (NBS) is the NIH's local portion of this systems effort and is an integrated enterprise-wide business system that incorporates finance, budget execution, travel, acquisitions, inventory, supply, and property functions through the use of commercial off-the-shelf software. The finance and travel portions of the system are in place. Currently being developed are business processes pertaining to acquisitions, inventory management, interagency agreements, and fixed assets. These additional areas will significantly expand existing functionality for accounts payable, accounts receivable, purchasing, and the projects module.

Enhancing the NIH Risk Assessment Program

The Office of Management and Budget (OMB) reissued Circular A-123 in December 2004 to reemphasize management's responsibility for effective and efficient controls on business operations. During FY 2005, NIH developed a comprehensive plan for enhancing its entire risk assessment and management improvement program, with emphasis on processes for identifying and correcting risks and vulnerabilities in financial operations as well as major programs and administrative activities. The NIH risk management program places greater emphasis on preventing problems by building performance indicators and controls into automated systems

and agency processes to provide early warning that management actions are needed. The new program also includes training for managers as well as personnel at the transaction level to ensure controls are in place and operating effectively.

Improved Grants Management Operations and Oversight

The NIH Extramural Research Program received the highest possible rating, "Effective," in the FY 2006 Program Assessment Rating Tool (PART) review by the OMB. Moreover, NIH continues to improve grants management operations in two areas—electronic government (e-government) and peer review of research grant applications.

e-Government. NIH extended its Electronic Research Administration (eRA) enterprise system to ensure that this end-to-end electronic processing of research grants is a collaborative endeavor of the full biomedical research community and NIH's Federal partners. On December 1, 2005, over 1,800 applications were transmitted electronically—a milestone toward accomplishing the PMA mandate in the area of grants management. Participation in cross-government efforts includes the Federal Grants.gov initiative, Grants Management Line of Business (a government-wide initiative under P.L. 106-107), and the Chief Information Officers Council. This eRA integration—80 percent complete and ahead of schedule—has created one of the largest Federal consolidations of grants management activities. eRA also enables NIH to innovate in information management. In FY 2005, NIH used advanced text data mining technology to begin developing knowledge management tools that will improve NIH reporting.

Peer Review. New electronic and management tools are helping NIH keep up with the fast pace of the scientific world, while preserving the rigor and fairness of its peer review system. Now NIH is initiating a pilot study to significantly shorten the duration of peer reviews of research grant applications. Focusing on one of the most promising but vulnerable groups of researchers—new investigators—the shortened process will save over 4 months for resubmitted grants. This will allow scientists to initiate their research sooner, to the public's benefit.

Hurricane Katrina. Grants management received an unexpected challenge from hurricane Katrina. Grantees at institutions in the disaster area required rapid assistance with situations ranging from the inability to make grant submission deadlines to damaged or destroyed research facilities. Multiple notices were issued to aid NIH grantees in the disaster area beginning as early as August 29, and a Frequently Asked Questions document was posted on September 14 at http://grants.nih.gov/grants/katrina/katrina_faqs.htm. This site provides comprehensive information on topics including delayed application submission, laboratory displacement, and supplemental funds for renovations, construction, and other destroyed research resources.

Improved Information Technology Efficiency and Effectiveness

NIH recognizes information technology (IT) as a vital resource necessary to advance its ongoing scientific programs and their support systems. As part of NIH's commitment to the efficient use of these resources, NIH undertook extensive IT infrastructure consolidations during FY 2003 and FY 2004. The consolidations included help desks, e-mail systems, wireless networks, network management, and directory services. Now complete, these consolidations are producing savings

and improving security, reliability, and service. An independent benchmark study, completed in July 2003, showed that consolidation of the help desks and e-mail systems produced a combined savings of $2.4 million annually. To identify opportunities for future improvement, NIH commissioned a benchmark study of the central NIHnet network environment that identified opportunities to potentially improve cost control and NIH is pursuing those opportunities. A benchmark study of telecommunications services is planned for FY 2006, with additional targets of opportunity identified there also.

Care for the Environment and Federal Real Property

In FY 2005, NIH completed the consolidation of the management and operation of NIH facilities into a single organization, the Office of Research Facilities Development and Operations. This office is responsible for the entire life cycle of NIH's owned and leased facilities from planning through development and construction to day-to-day operations and long-term stewardship. The Research Facilities organization is leading the development of the NIH high-containment biomedical research facilities under construction in Bethesda and Fort Detrick and at the Rocky Mountain Laboratories in Hamilton, Montana. This effort involves extensive research into the best methods for bio-containment, as well as the development of peer-reviewed building and system performance criteria.

NIH continues a legacy of environmental stewardship that contributed to NIH being named one of the Greater Washington Region's Best Workplaces for Commuters by the Environmental Protection Agency. This recognition acknowledges NIH's efforts to reduce traffic congestion and air pollution in the region by providing outstanding commuter benefits for its employees. The NIH sponsored the first government electronics recycling event, which set a record for the highest single day recycling collection in the State of Maryland. The NIH also received the prestigious White Oak award from the Maryland Department of Natural Resources and the Gold Leaf award from the International Society of Arboriculture in FY 2005 for excellence in forest conservation and land development. The NIH in conjunction with DHHS has also sponsored environmental workshops for the last 4 years to share environmental best management practices. Beginning in 2006, the workshop is being adopted by the Office of the Federal Environmental Executive as a government-wide symposium with the same purpose.

NIH Physical and Personnel Security Initiatives

During FY 2005, NIH activated its Perimeter Security System for the Bethesda Campus and began construction of the final two elements associated with the total perimeter package. Specifically, construction began on the new Commercial Vehicle Inspection Facility and also the Gateway Center. These will be permanent facilities for screening vehicular and pedestrian visitor traffic entering campus. In FY 2006, the NIH will put into full operation the state-of-the-art Commercial Vehicle Inspection Facility, which will greatly enhance the effectiveness and efficiency of screening of large vehicles entering campus. A similar perimeter security system will be activated at the Rocky Mountain Laboratories in Montana. In FY 2007, the NIH will put into full operation a new Gateway Center visitor facility to expedite the processing of visitors and non-commercial vehicles to the NIH Campus. The Gateway Center will be the final piece of the comprehensive perimeter security system for the Bethesda campus and will include a

350-space parking garage designed to reduce the need for vehicle screening, thus making the entry process more efficient for both the NIH and its visitors. The NIH will also implement the necessary personnel security processes and procedures to comply with the requirements of a Homeland Security Presidential Directive for a common identification standard for Federal employees and contractors. This implementation will extend into FY 2007, when NIH will issue "Smart Cards," i.e., comprehensive identification cards, to all employees and contractors in accordance with DHHS guidance and schedules.

RESEARCH COORDINATION COUNCIL

Through its participation in the Department's Research Coordination Council (RCC), NIH will continue to ensure that planned FY 2007 research, demonstration, and evaluation (RD&E) activities are coordinated with other components of DHHS and align with the Secretary's 500-day plan that includes strategies to help fulfill the President's vision of a healthier and more hopeful America.

NIH supports research on a range of RCC themes including Working Toward Independence; Rallying the Armies of Compassion; Promoting Active Aging and Improving Long-Term Care; 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. Recent RCC meetings on "Research on Childhood Obesity" and "Research in Support of 2010 Dietary Guidelines for Americans" focused on the Strategic Plan for NIH Obesity Research.

National Institutes of Health
RD&E Funding by Research Theme
FY 2007
(Dollars in Thousands)

Total Budget

	FY 2007 Estimate
I. Working Toward Independence	$0
II. Rallying the Armies of Compassion	9,000
III. No Child Left Behind	3,600
IV. Promoting Active Aging and Improving Long-Term Care	0
V. Protecting and Empowering Specific Populations	5,250
VI. Helping the Uninsured and Increasing Access to Health Insurance	0
VII. Realizing the Possibilities of 21st Century Health Care	28,200
VIII. Ensuring our Homeland is Prepared to Respond to Health Emergencies	228,300
IX. Understanding Health Differences and Disparities---Closing the Gaps	46,400
X. Preventing Disease, Illness, and Injury	156,800
XI. Agency-Specific Priorities 1/	27,933,452
Subtotal, Research	28,411,002
Buildings and Facilities	89,001
Total Budget	28,500,003
Superfund	78,414
NIH Program Total	28,578,417

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

FY 2007 BUDGET POLICY

The FY 2007 Request for the NIH is $28,587 million at the total program level, the same as the FY 2006 program level. Included in this level is $78 million for the Superfund Research Program. The NIH program level also includes $150 million for the Type I Diabetes Initiative appropriated by Public Law 107-360. The FY 2007 request to the Labor, Health and Human Services, Education, and Related Agencies Subcommittee is $28,350 million.

Biodefense

NIH will continue implementation of the long-range strategic plan for biodefense research to enhance the ability of the Nation's health care system to effectively respond to bioterrorism. The total Biodefense budget is $1,891 million, an increase of $110 million and 6.2 percent. Within this increase, NIH will direct $160 million, an increase of +$110 million over the FY 2006 program level of $50 million, to an Advanced Development fund. This initiative will support efforts to work with academia and industry to develop candidate countermeasures from the point of Investigation New Drug Application (INDA) to the level that these candidate countermeasures could be eligible for acquisition by Project BioShield. The FY 2007 request would support the advanced development of a third-generation anthrax vaccine, anthrax therapeutics, and antivirals for smallpox and hemorrhagic fevers.

AIDS

The FY 2007 Request includes $2,888 million to support basic research and to develop vaccines and improve treatments and prevention strategies against HIV/AIDS. This reflects a decrease of –0.5 percent or -$15.172 million, for a total of $2,888 million. 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 2007.

NIH Priorities

In this budget request, NIH provides resources in the Research Project Grant (RPG) mechanism to preserve to the greatest extent possible the ability of scientists to obtain individual support. NIH has also chosen to carefully invest in trans-NIH strategic initiatives, similar to the investments we have made in obesity research and the NIH Blueprint for Neurosciences. In the FY 2007 Request, we have identified the following strategic priorities:

Enhanced Support for New Investigators -- NIH must sustain a vibrant, creative research workforce, including sufficient numbers of new investigators with new ideas and new skills, such as interdisciplinary research skills. The engines that drive the research enterprise are talented, creative and dedicated research personnel. We cannot again risk losing a "class" of young researchers, as we did in the mid-1990's, by allowing new investigators to become utterly discouraged by the difficulty of obtaining funding for their research ideas, and leaving science. In the FY 2007 Request, NIH will invest $15 million in a new program—Pathways to Independence--that will provide increased support for new investigators.

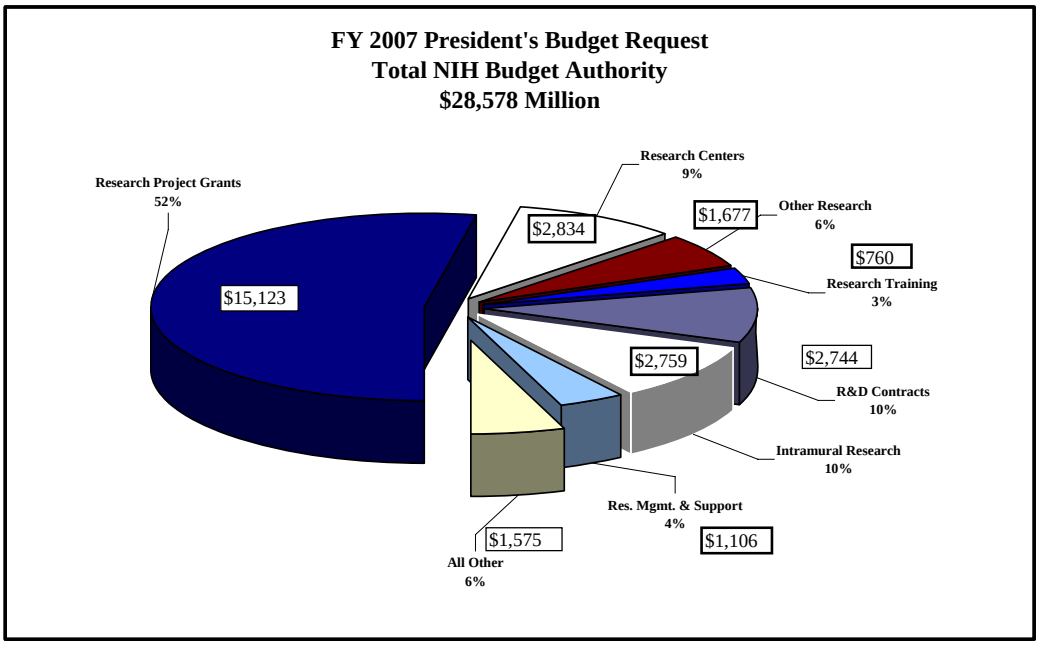
NIH Roadmap for Biomedical Research – NIH plans to continue to increase its support for the Roadmap in FY 2007. The NIH Roadmap is an incubator for new ideas and initiatives that will accelerate the pace of discovery. In FY 2007, NIH will direct $443 million towards the Roadmap initiatives, an increase of +$113 million over the FY 2006 Appropriation. Of the $443 million total, $111 million will be provided by the NIH Director's Discretionary Fund (DDF), and the remaining $332 million will be provided by the Institutes and Centers (ICs). The IC contribution to support these trans-NIH research goals is estimated to be 1.2 percent of each individual budget request for FY 2007.

Genes, Environment and Health Initiative -- The Department of Health and Human Services is proposing a forward-looking initiative to benefit the health of all Americans. Recognizing that health and disease are due to the complex interplay of genetic and environmental factors, including diet and physical activity, the Initiative's two-pronged approach would lead directly to the identification of major genetic susceptibility factors for common diseases like heart disease, stroke, osteoarthritis, cancer, diabetes, and Alzheimer's disease, while simultaneously advancing the development of new technologies to assess the contribution of diet, physical activity, and environmental exposures to the causation of these illnesses. Like the Human Genome Project (the successful effort to sequence the human genome) and the International HapMap Project (the successful effort to catalog variation in the human genome) that laid the groundwork necessary for it, this new Initiative would catalyze the development of U.S. biotechnology and would make the data it generates rapidly and freely available to researchers in both the public and private sectors, speeding the development of new strategies and tools to fight disease. To prepare effectively for this initiative, the National Institutes of Health (NIH) has planned several pilot studies, which begin in FY 2006. In FY 2007, NIH will direct $68 million towards this multiyear initiative.

Clinical and Translational Sciences – In order to accelerate the benefits of the major research investment of the past several years, NIH will undertake a bold new program to reshape our support for clinical and translational sciences. Our goal is to provide the academic home and integrated resources necessary to advance a new intellectual discipline of clinical and translational sciences, create and nurture a cadre of well-trained investigators, and advance the health of the nation by transforming patient observations and basic discovery research into clinical practice. This program will take elements of existing NIH programs for clinical research, primarily the General Clinical Research Centers in the National Center for Research Resources (NCRR), as well as Roadmap initiatives in the Reengineering the Clinical Research theme and combine them in a way that we hope will create better and faster bridges between research findings and clinical practice. In addition to several full awards, NIH plans to award planning grants for this activity in FY 2006, and from FY 2007 to FY 2012, the program will increase as existing GCRCs complete their current funding cycles and recompete as these transformational awards. In FY 2007, NIH has also directed an additional $3 million to the National Center for Research Resources for this high-priority program.

Management Innovations – NIH will continue to pursue innovative ways to improve the management of its biomedical and behavioral research portfolio. The newly formed Office of Portfolio Analysis and Strategic Initiatives (OPASI) will develop methods to assist the agency in

assessing its large and complex portfolio, coordinate trans-NIH evaluation efforts, and provide a transparent process for identifying important scientific initiatives that cut across or fall between the missions of institutes and centers. Selected initiatives will be supported through a Common Fund that will build on the funding base of the NIH Roadmap. Proposals for topics to be funded through the Common Fund will be selected based on review and advice obtained from scientific and public representatives from existing chartered NIH advisory committees and the NIH scientific leadership. To ensure that there are sufficient funds for continuous development of new trans-NIH efforts, it is expected that initiatives funded through this process will be time limited. OPASI represents a bold and innovative approach that will enhance NIH-wide planning and priority setting.



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, remains a high priority for the National Institutes of Health. The FY 2007 Request would support an estimated 9,337 competing RPGs, for $3.3 billion, an increase of 275 competing RPGs over the FY 2006 Appropriation. In the FY 2007 Request for NIH, the average cost of a competing RPG will not increase over the FY 2006 Appropriation. The apparent decrease in average cost in FY 2007 is the result of an extremely large cohort of AIDS clinical trials and G-8 HIV Vaccine awards cycling from competing into noncompeting status. 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.

The FY 2007 request would support 1,373 Research Centers, for $2.8 billion, an increase of $62 million, or 2.3 percent.

Other Research increases by 1.2 percent. Within the Other Research mechanism, Research Careers increases by $21 million, including $15 million for the new Pathways to Independence program to support new investigators, as described above on page 63. This program is consistent with the recommendations contained in two recently-published reports from the National Research Council, "*Bridges to Independence: Fostering the Independence of New Investigators in Biomedical Research*" (March, 2005) and "*Advancing the Nation's Health Needs: NIH Research Training Programs"* (May, 2005). This new career transition award program will promote the initiation of independent research careers. The award is anticipated to provide up to five years of support consisting of two phases. The initial phase will provide 1-2 years of mentored support in the Research Careers mechanism, followed by 1-3 years of independent support as a Research Project Grant, contingent on securing an independent research position.

In the FY 2007 Request for NIH, stipends for trainees supported by the Ruth L. Kirschstein National Research Service Award (NRSA) will remain at the FY 2006 Appropriation levels. No increases are provided for other components of the NRSA training programs, such as tuition or health benefits. In the FY 2007 request, training remains at approximately the same level as the FY 2006 Appropriation. The FY 2007 Level will support 17,499 Full-Time Training Positions (FTTPs), approximately the same as the FY 2006 Appropriation.

Research and Development (R&D) contracts increase by $44 million and 1.6 percent compared to the FY 2006 Appropriation. This increase is the result of the increase in the Genes, Health and Environment initiative and increases in the Program Evaluation set-aside.

Intramural Research decreases in total by -0.3 percent. Research Management and Support increases by $14 million, or 1.3 percent. NIH must have the necessary resources to ensure good stewardship of its research portfolio, including improvements in data management and security systems.

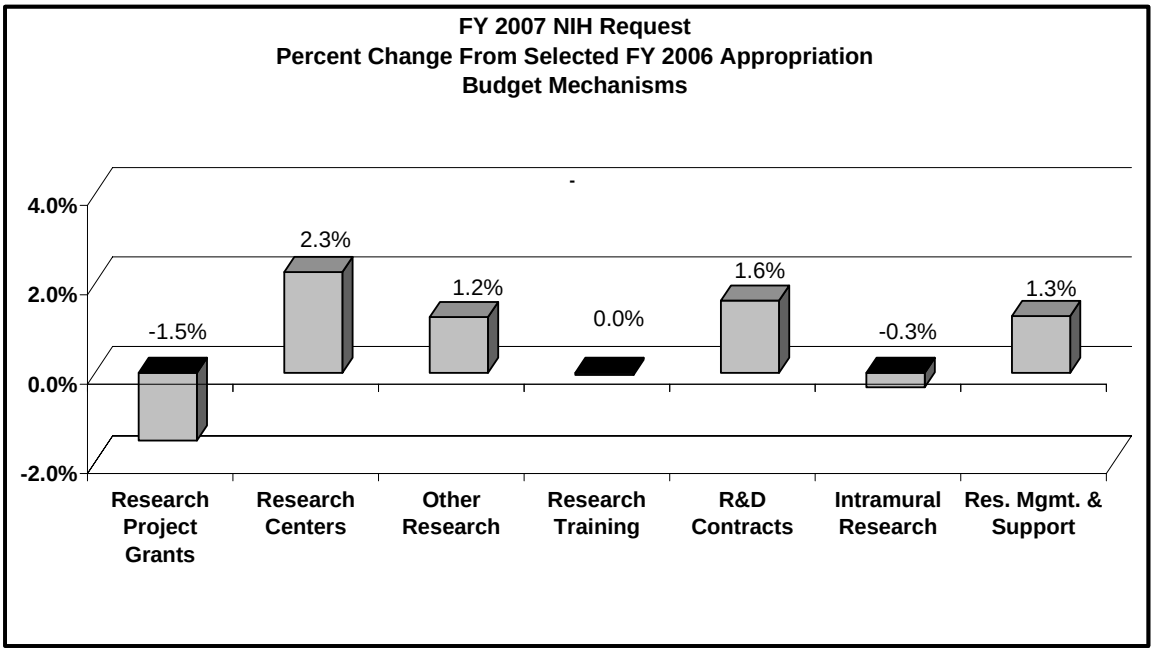
An integral element to developing and supporting a robust extramural biodefense research program in the U.S., is to build and provide to extramural researchers the use of the specialized, high-containment labs that they need in order to conduct research on the most dangerous and infectious pathogens 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 2007, NIH is requesting a total of $25 million to construct additional BSL-3 laboratories and to renovate existing laboratories to meet current BSL-3 standards, including providing the capacity to support Good Laboratory Practice (GLP) research processes within selected BSL-3 laboratories. Consistent with the FY 2006 Appropriation, no funds are provided for non-biodefense extramural construction.

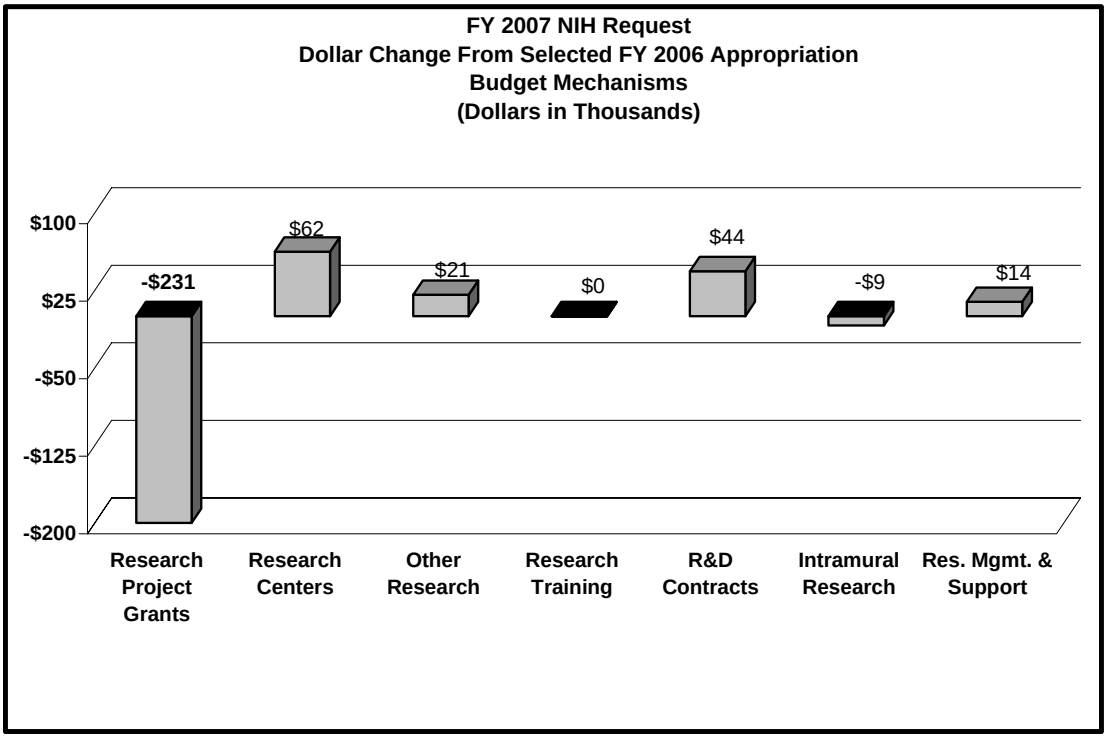
The Buildings and Facilities mechanism remains at $89 million, the same as the FY 2006 Appropriation. The appropriation request for Buildings and Facilities is $81 million, also the same as the FY 2006 appropriation. These funds will allow NIH to fund ongoing programs for essential safety and regulatory 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. Funds for the NCI-Frederick facility remain at $8 million, the same as the FY 2006 Appropriation.

The Office of the Director reflects two comparable adjustments: The FY 2005 column reflects a shift of the nuclear/radiological countermeasures research funds from the Public Health and Social Services Emergency Fund in the Department of Health and Human Services to the NIH Office of the Director (OD). In FY 2006, a comparable adjustment of $50 million has also been made between the National Institute of Allergy and Infectious Diseases and the OD, as funds for advanced development of biodefense countermeasures will now be reflected in the OD.

With this comparable adjustment for advanced development in FY 2006, the appropriation request for Office of the Director (OD) increases by $140 million, or 27 percent, for a total of $668 million. Of this amount, $111 million has been reserved in the NIH Director's Discretionary Fund for the NIH Roadmap for Medical Research, an increase of +$29 million over the FY 2006 Appropriation. NIH will also direct an additional $1 million to the Office of Portfolio Analysis and Strategic Initiatives. Support for Advanced Development for biodefense countermeasures increases by +$110 million over the FY 2006 Appropriation, for a total of $160 million. Funding for Nuclear/Radiological and Chemical Countermeasures research will remain at $96 million, the same as the FY 2006 Appropriation.





Other Key Issues

In support of the Department's Pandemic Influenza Preparedness Plan, the FY 2007 President's Budget requests an additional $17 million to support specific initiatives in pandemic influenza research. Research activities that will be supported by these funds include assisting in the development and testing of candidate vaccines and drugs produced by Vietnam and other countries with endemic avian influenza, expanding the clinical trials infrastructure and research in Southeast Asia, and conducting human-animal interface studies, including the surveillance of diseases in animals in SE Asia. Overall NIH spending on influenza in FY 2007 is estimated to increase to $199 million, $35 million over the FY 2006 estimate.

NIH Management and Information Technology

Unified Financial Management System (UFMS). 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. UFMS has reached a major milestone in April 2005 with the move to

production for the Center for Disease Control (CDC) and the Food and Drug Administration (FDA). NIH's FY 2007 budget includes $2.190 million for this purpose.

Accounting Operations. Operations and Maintenance (O & M) activities for UFMS commenced in FY 05. The Program Support Center will provide the O & M activities needed to support UFMS. The scope of 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's FY 2007 budget includes $3.567 million for this purpose.

Automating Administrative Activities. HHS agencies have been working to implement automated solutions for a wide range of administrative activities. As UFMS development and implementation move toward completion, there are added opportunities to improve efficiency through automating the transfer of information from administrative systems to the accounting system. NIH's FY 2007 budget includes $4.098 million to support coordinated development of these improved automated linkages and administrative systems.

ENTERPRISE INFORMATION TECHNOLOGY FUND

The NIH FY 2007 request includes funding to support the President's Management Agenda Expanding E-Government and Departmental enterprise information technology initiatives. Operating Division funds will be combined to create an Enterprise Information Technology (EIT) 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 initiatives promote collaboration in planning and project management and achieve common HHS-wide goals. Examples of HHS enterprise initiatives funded by the EIT Fund are Enterprise Architecture, Capital Planning and Investment Control, Enterprise E-mail, Grants Management Consolidation, and Public Key Infrastructure."

Also 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). Funds are also included for implementation of Homeland Security Presidential Directive #12, requiring the use of "smart cards" for employees and other security measures.

NIH Management

NIH Institutes and Centers will pursue a variety of strategies to minimize administrative costs, including analyzing administrative processes and looking for ways to streamline and identify

best practices, increasing emphasis on portfolio evaluation and review, and finding savings in supplies, equipment, and other costs.

The workforce at NIH is one of its greatest assets because of the large number 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.

FULL-TIME EQUIVALENTS (FTEs)

	FY 2005 Enacted	FY 2006 Appropriation	FY 2007 Request	Change FY 2006 /FY 2007
Ceiling	**16,868**	**17,326**	**17,446**	**120**
Ceiling Exempt	**13**	**10**	**10**	**0**
Total NIH	**16,881**	**17,336**	**17,456**	**120**