Over the last half century, the nation’s investment in the NIH yielded myriad scientific achievements, many of which improved the length and quality of human life. Many more of these publicly funded research efforts are the basis for countless future advances in science and improvements in health. One of the most visible examples, the completion of the sequencing of the human genome, is creating heretofore un-imagined opportunities to explore the full spectrum of human biology in both health and disease.

To build on past accomplishments, further accelerate the pace of scientific discovery, and spur the translation of findings into newer and even better ways to prevent, diagnose, and treat disease, in September 2003, NIH leadership launched a set of initiatives collectively known as the NIH Roadmap for Medical Research. The NIH Roadmap targets research investments that promise to yield far-reaching dividends in medical knowledge. The initiatives cut across the missions of Institutes and Centers, integrate the work of multiple disciplines, and are expected to lead to advancements that address the most pressing health needs and medical concerns of the American people.

Aware of the significant shift of disease burden that has taken place in recent decades, NIH is increasingly focused on chronic diseases, which have overtaken acute conditions as the nation’s leading killers – conditions such as cardiovascular disease, stroke, hypertension, and cancer. NIH will also expand a major NIH-wide initiative begun last year to uncover the knowledge needed to prevent and treat one of the nation’s most pressing health problems – obesity. The NIH also remains focused on reducing or eliminating health disparities among racial, ethnic, and disadvantaged populations.

The NIH will continue efforts to protect the Nation against potentially lethal bioterrorist acts through basic research on the infectious diseases that constitute the highest threats and developing vaccines, diagnostics, and therapeutics to address them. We will also maintain a strong focus on other infectious diseases that threaten the health of the nation, such as SARS, West Nile Virus, influenza, malaria, and tuberculosis as well as the persistent problem of HIV/AIDS.

As the most influential force in the U.S. biomedical research community, NIH exercises its leadership by continually surveying public health needs and the scientific landscape to identify new biomedical areas that require attention and new opportunities for progress. To maintain the vibrancy of our nation’s scientific enterprise, NIH also actively supports strong basic and clinical research training programs. NIH-funded programs are unique in both igniting and complementing private sector research and development efforts. NIH tackles studies for which the risks are too high or the fiscal incentives too low to attract private investment. These
research arenas span the health care spectrum, ranging from basic studies and technology development to the evaluation of non-commercially viable, yet critical, 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 NIH-led investigations 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.

NIH supports an extramural research community of an estimated 212,000 research personnel who are affiliated with approximately 2,800 organizations, including universities, medical schools, hospitals, and other research facilities in all 50 states as well as the District of Columbia, Puerto Rico, Guam, the Virgin Islands, and international venues. NIH’s 27 Institutes and Centers are based at the world’s largest campus for biomedical research, where an in-house (intramural) research enterprise is staffed by a cadre of distinguished clinicians and scientists. This intramural program will utilize the nearly completed state-of-the-art Clinical Research Center, providing the nation and the world with an unparalleled capacity for rapid response to serious health challenges.

To maintain a research portfolio that balances public health needs and scientific opportunities, NIH seeks public input through multiple channels, including the Advisory Committee to the Director and the NIH Council of Public Representatives. A two-tier system of advisory bodies and specialized review committees guarantees funding of the best applications from among the nearly 50,000 research and training applications reviewed annually. The general public has direct access to a wealth of reliable and readily understandable health information through a variety of NIH contact points, including the very popular NIH web site (www.nih.gov). Also featured at this site are ongoing clinical studies, which underscore NIH’s commitment to translate research discoveries into treatment strategies for use by physicians on the front lines.

**NIH Roadmap**

NIH and biomedical and behavioral research are at a critical juncture in their history, a turning point that requires new strategies. While NIH has had considerable success bringing to the public novel means to prevent, diagnose, treat, and even cure diseases, many of the most important questions in health care practice are more complex than even a decade ago. Addressing these questions requires change in the methods for conducting research, in the teams that carry out the studies, and in the way we support the scientific enterprise.

To determine how to meet these challenges and to accelerate the pace of discovery and the translation of findings into interventions for public benefit, over the past year, NIH leaders consulted broadly with its many stakeholders and engaged in extensive internal deliberations. The product of this historic trans-NIH effort is a series of initiatives known collectively as the NIH Roadmap for Medical Research.
Developed with input from more than 300 leaders in academia, industry, government, and the public, the NIH Roadmap initiatives focus on major opportunities and gaps in the research agenda that no single institute at NIH can tackle alone but that the agency as a whole must address. By addressing the identified opportunities and gaps, NIH hopes to remove some of the biggest roadblocks that are keeping research findings from reaching the public as swiftly as possible. In September 2003, NIH announced a Roadmap strategy that features 27 initiatives to be carried out by nine implementation groups under three themes–New Pathways to Discovery, Research Teams of the Future, and Re-engineering the Clinical Research Enterprise.

NIH has begun to implement the initiatives in fiscal year 2004. Some initiatives that build upon existing research efforts are expected to achieve their goals rapidly, while other newer or more complex endeavors are expected to continue for more than a decade and are expected to take years to come to fruition.

Under **New Pathways to Discovery**, the NIH Roadmap aims to quantify and catalog complex biological systems and seeks to build a better “toolbox” for today’s biomedical researchers. Just as systemic treatises on anatomy and the perfection of the microscope in the 19th Century were key to modern medicine in the 20th Century, comprehensive databases of quantitative information on biochemical pathways and molecular interactions and tools to capture and manage that information will be pivotal to advances in 21st Century health care. A few of the initiatives in this area are:

- **National Technology Centers for Networks and Pathways.** These Centers will be established to investigate the array of intricate and interconnected pathways that enable communication among genes, molecules, and cells. Researchers at the Centers will discover many more pathways, decipher how pathways are integrated in humans and other complex organisms, determine how disturbances in pathways lead to disease, and learn what might be done to restore disturbed pathways to their normal functions. New tools will also be created to carry out this research. One of the central components of pathways is the set of proteins that our bodies make based on instructions from our genes (the human proteome). To better understand the proteome, innovative tools must be developed that will enable researchers to determine the amounts, locations, and interactions of large numbers of individual proteins within a single cell in real time. Another critical focus is providing researchers with novel analytical tools to better understand the metabolic components (e.g., the carbohydrates, lipids, amino acids, and other products of biological change within an organism) of networks within the cell, which are commonly referred to as the metabolome.

- **National Centers for Biomedical Computing.** Increasingly, the most fruitful scientific and technical approaches to biomedical and behavioral research involve bioinformatics and computational biology as well as experimentation. Because the science of information

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1Every gene encodes instructions for a unique protein, and the functional expression of the human genome is the human proteome.
management has become an integral element of scientific investigation, to meet the infrastructure needs of modern biomedical and behavioral research, the NIH is embarking on a long-term initiative to establish an integrated national biomedical computing environment. The National Centers for Biomedical Computing will enable researchers to share data gathered from large experiments, allowing them to work together more efficiently to tackle unsolved mysteries. The partnerships cultivated by the Centers will produce, validate, and disseminate tools and computational environments that will be useful to a broad spectrum of biomedical researchers across the nation.

- **Protein Production Facilities.** The NIH Roadmap initiative is focusing on the long-standing challenge of protein structure through the development of rapid, efficient, and dependable methods to produce protein samples that scientists can use to determine the three-dimensional structure, or shape, of a protein. Knowledge of these protein structures is key to understanding many diseases because if the shape of even one protein happens to go awry, there can be major consequences for human health. However, extremely large amounts of high-quality protein are needed to perform the difficult experiments involved in helping researchers understand what role protein shape plays in health and disease. The process of generating research-grade protein currently is a slow, hit-or-miss process. At the new Protein Production Facilities, scientists will work to streamline methods so that specific proteins can be produced and analyzed faster.

- **Nanomedicine Centers.** With the advent of nanotechnology, which involves the creation and use of materials and devices as small as molecules and atoms, researchers can begin to define, categorize, and map interactions between and within molecules in engineering terms. These are crucial steps toward understanding the rules of biological design that will, in many years’ time, enable scientists to build synthetic biological devices, such as miniature, implantable pumps for drug delivery, or tiny sensors to scan for the presence of infectious agents, or metabolic imbalances that could signify disease.

Because the complexity of today’s biomedical and behavioral research increasingly requires scientists to move beyond the confines of their own disciplines, under the theme, **Research Teams of the Future,** the NIH Roadmap is encouraging scientists and scientific institutions, including NIH itself, to test alternative models for conducting research. The need for new organizational models that support team science is driven by the convergence of biological, physical, and information sciences. For example, imaging research often requires radiologists, physicists, cell biologists, and computer programmers to work together on integrated teams. Accelerating the pace of discovery also requires new models that encourage risk-taking and novel partnerships such as those between the public and private sectors. In addition, there are new approaches for training the research workforce in interdisciplinary team science. Examples of initiatives in this arena include:

- **Exploratory Centers for Interdisciplinary Research.** These centers are expected to help scientists overcome the often substantial barriers to establishing interdisciplinary research
efforts. As scientific capabilities move forward, increasingly complex questions arise, and addressing such complex questions often requires the convergence of perspectives from multiple disciplines. In recognition of the difficulty of establishing interdisciplinary research efforts, the NIH Roadmap initiative will support planning activities for groups of researchers who, if successful, will later apply for support for Interdisciplinary Research Consortia. Success at the planning stage is defined as combining aspects of individual disciplines to provide a new approach to solving a problem that is likely to yield insights that could not have been achieved by an isolated laboratory or simply bringing together researchers from different disciplines to focus on a circumscribed problem. Successful interdisciplinary researchers will integrate several disciplinary approaches in a more sustained and systematic fashion.

- **Interdisciplinary Health Research Training: Behavior, Environment, and Biology.** A new program within the NIH National Research Service Award (NRSA) mechanism, the Interdisciplinary Health Research Training initiative will address training issues critical to interdisciplinary team science. This initiative aims to develop a cadre of scientists with the requisite skills and knowledge to integrate multiple scientific approaches and to work in interdisciplinary research teams to solve complex health problems. The new awards will support postdoctoral training programs that provide formal course work and research training in a new field to individuals who already hold an advanced degree in another field. The postdoctoral fellows and the program faculty are expected to represent multiple disciplines, one of which must be in the behavioral or social sciences.

- **NIH Director’s Pioneer Awards.** Also as part of the NIH Roadmap, the agency is launching awards that will encourage investigators to pursue innovative, unexplored avenues of research that are high risk, but also possess a significant chance for truly groundbreaking discoveries. For the most part, the NIH supports research projects, not individual scientists. However, this new award mechanism will enable NIH to support a highly select group of individuals who have the potential to make extraordinary contributions to medical research. Individuals will be evaluated in terms of their exceptional creative abilities, potential for ground-breaking discovery, evidence of focused and skillful habits of mind that predict perseverance, and prospects for making seminal biomedical research advances.

Under the theme **Re-engineering the Clinical Research Enterprise**, NIH is launching a set of initiatives to accelerate and strengthen the national clinical research enterprise. Today, there is a pressing need for innovative approaches that yield clinically relevant results even more quickly. Future efforts to translate scientific discoveries into health care interventions require new partnerships within diverse clinical settings and communities, improved systems, and updated policies. NIH Roadmap initiatives will incorporate modern information technology, promote improved integration of current and new clinical research networks, stimulate the development of technologies to improve the assessment of clinical outcomes, enhance the coordination of clinical research policies, including human subjects protections, improve clinical research workforce training, and provide essential core research infrastructure, support, and services. A few of the NIH Roadmap initiatives in this area are:
• **Integration of Clinical Research Networks.** Large clinical studies are often best conducted through groups of dispersed investigators equipped with tools that facilitate collaboration and information sharing. Most clinical research networks operate independently of each other, often focused on a single problem or disease. Promoting the integration of diverse clinical research networks will significantly enhance the efficiency and productivity of the Nation’s clinical research enterprise. Also, standardized lexicons for data gathering and reporting and compatible information technologies will enable seamless data and sample sharing across studies and would allow researchers to broaden the scope of their research and even ask questions that could not have otherwise been addressed. An integral part of this initiative is a plan to foster a *National Electronic Clinical Trials and Research Network (NECTAR)* to maximize informatics connectivity among extant and newly created clinical research networks. NECTAR will create the kind of electronic information sharing infrastructure that will support more efficient business practices and processes across and between networks.

• **Clinical Research Policy Coordination Initiative.** The NIH is establishing a Clinical Research Policy Coordination Initiative (CRPCI) to create a focal point for working to promote the coordination and, where appropriate, the streamlining of policies and requirements concerning the conduct and oversight of clinical research. The wide variability in regulations and procedures across Federal funding agencies affects the efficiency and effectiveness of our system of clinical research. The CRPCI will examine an array of issues and activities on behalf of all NIH ICs and help develop coordinated policies and practices and new tools for compliance that take account of the goals and points of view of NIH’s varied organizational components and stakeholders. This effort will focus on improving the protection of human subjects by aiming to ensure policies are both effective and efficient.

• **Clinical Workforce Training.** A nationwide pool of community-based clinicians, who are prepared to participate as partners in clinical research, will help accelerate scientific discovery. In this regard, the NIH plans to establish a cadre of National Clinical Research Associates made up of physicians, dentists, nurses, statisticians, epidemiologists, clinical pharmacologists, study coordinators, psychologists, data managers, and other clinical professionals. The Associates will receive specialized training in clinical research and will play a critical role both in advancing the development of health care interventions and in disseminating research findings to the community.

Taken together, the components of the NIH Roadmap are an ambitious vision for a more efficient and productive system of medical research, with the goal of improving the length and quality of human life. Moreover, the development and implementation of the NIH Roadmap represents a new approach to portfolio management. Building on earlier experience with trans-NIH endeavors, the NIH Roadmap planning process sets a new standard for responding to emerging needs and opportunities that do not fit clearly within the mission of a single or a small group of Institutes and Centers.
More Challenges Ahead

Chronic diseases now account for 70 percent of all deaths and 75 percent of today’s health expenditures. Ironically, much of the cause of this development is the result of the Nation’s success in battling acute and lethal diseases – a success that has led not only to a shift in the balance of disease incidence but a significantly higher life expectancy for people in this country. As the share of the U.S. population over the age of 65 significantly increases, so has the segment of the population most subject to chronic disease.

**Obesity.** One of this century’s most daunting chronic health challenges is obesity – a major health problem in its own right and a strong risk factor for serious diseases such as type 2 diabetes, heart disease, stroke, certain cancers, osteoarthritis, liver disease, sleep apnea, and depression. A staggering number of adults in the U.S. are overweight (65 million) or obese (61 million). The tripling of the number of overweight children since 1970 has been accompanied by an alarming increase in children with type 2 diabetes.

Encouragingly, the outcome of the Diabetes Prevention Program (DPP) clinical trial indicates that moderate weight loss and activity can significantly delay or prevent obesity-associated health conditions. Research on different dietary components (such as the amount and type of fats, carbohydrates, and proteins) will help lay a foundation for improved dietary advice. The long-term evaluation of the health consequences of different diets (including the popular Atkins diet) is especially important for addressing the proverbial question: “What should I eat?”

To address the obesity problem, the NIH is initiating research at many levels – from the societal and individual to the molecular. These efforts will be aimed at discovering new ways to modify lifestyle through behavioral and environmental interventions. Although genetic factors play a role in predisposing individuals to obesity and related health problems, the dramatic increase in the prevalence of obesity in the past few decades points to the preeminence of environmental factors in overeating and physical inactivity of susceptible individuals. Successful interventions need to be designed both to promote individual behaviors that improve diet as well as increase physical activity and to modify home, school, workplace or community environments to make these settings more conducive to the widespread adoption of more healthful eating and physical activity behaviors.

To complement lifestyle interventions, NIH also hopes to delve into the pharmacologic, surgical, and other biological approaches to treating obesity. We already know that an elaborate network of hormones and other molecules participate in the signaling pathways that connect the brain, gut, fat cells, and other parts of the body. We also know that these pathways function to achieve an integrated control of energy balance. As obesity develops, the same regulatory systems that maintain the exquisite balance between energy intake (i.e., calories from food) and energy expenditure adjust to defend vigorously the higher weight, thus thwarting an obese individual’s attempt to lose weight and keep off pounds. Basic research by NIH investigators on hormones produced by fat cells and other factors in energy metabolism is beginning to offer tantalizing
hypotheses as to how the body’s innate regulatory systems may make weight loss and maintenance so arduous.

As hormones and molecules are found to contribute to sustaining energy balance, they will become “targets” for drug development. Drugs that home in on one of these targets could beneficially affect appetite, food absorption, or energy expenditure. Genetic studies provide yet another avenue to the discovery of novel molecules and pathways linked to obesity. Additionally, genetic studies may form the basis for selection of a particular treatment or preventive strategy optimized for an individual patient or subpopulation. For example, in one rare form of obesity that is caused by deficiency of the hormone leptin, replacement therapy with leptin is extremely effective in weight loss. Tailored treatments may likewise prove optimal for racial groups with a disproportionate amount of obese individuals, such as the American Indian population.

Health disparities. Despite tremendous medical advances and improved public health in recent decades, African Americans, Hispanics, American Indians, Alaska Natives, Asian and Pacific Islanders, and other medically underserved communities in the U.S. continue to suffer an unequal burden of illness, premature death, and disability. In October 2003, NIH released an updated version of its Strategic Plan to eradicate health disparities for public comment. The Plan defines a broad framework for future research efforts that acknowledges the multi-factorial genesis of health disparities and, thus, requires a coordinated interdisciplinary effort. The Strategic Plan has three main goals: (1) research to investigate the development and progression of diseases and disabilities that cause disparities in health in minority and other populations; (2) research infrastructure to increase minority health and health disparities research training, career development, and institutional capacity; and (3) public information and community outreach to ensure the public, healthcare professionals, and research communities are informed about the latest advances in health disparities research.

Infectious diseases. Infectious diseases are the most frequent cause of death worldwide and the third leading cause of death in the U.S. The NIH has long played a leading role in conducting and supporting research on infectious diseases and the immune system, with emphasis on emerging and re-emerging diseases such as HIV/AIDS. This role has evolved and expanded significantly with the tragic events of September 11, 2001. The subsequent anthrax attacks and, more recently, outbreaks of pathogens such as the SARS virus, further underscore the need to accelerate the development of effective measures to counter infectious diseases and other potential agents of bioterror, including chemical, radiologic, and nuclear.

Biodefense. NIH efforts advanced the first vaccines for anthrax and Ebola and next-generation vaccines against smallpox to the stage of initial clinical trials. NIH researchers also developed a rapid test for the presence of antibodies to smallpox that is 5-10 times more sensitive than the standard technique.

The NIH is working to expand both basic and clinical research on infectious diseases with potential for use as agents of bioterror. Ongoing and future biodefense research includes pre-
clinical development of vaccines for dengue virus, botulism, plague, and other threats; the screening and testing of antibiotics, antivirals, and antitoxins against all classes of biological pathogens including inhalation anthrax, and smallpox; creation of an “encyclopedia” of innate immunity—a comprehensive and detailed picture of the body’s essential first line of defense against infectious diseases; and the sequencing and analysis of the genomes of potential agents of bioterror.

NIH-supported research also made great strides in revealing the genetic trickery of potential agents of bioterrorism, including anthrax, plague, and many others. Genome sequencing projects are ongoing for at least one strain of every bacterium, virus, or protozoan on the list of Category A, B, and C priority pathogens, as a result of a coordinated Federal effort with the Department of Energy, the Centers for Disease Control and Prevention (CDC), the U.S. Department of Agriculture, and the National Science Foundation in conjunction with international partners. In ongoing analyses of the already sequenced smallpox genome, NIH-supported scientists already identified five genes whose protein products may be good targets for drugs that would stop smallpox infection.

To ensure capacity to carry out this research safely and efficiently, steps are also being taken to provide the appropriate research infrastructure. The NIH initiated plans for the renovation and construction biosafety level (BSL)-3 and BSL-4 facilities. In the extramural research community, this includes support for National Biodefense Laboratories and Regional Centers of Excellence in Biodefense and Emerging Diseases Research. The plans also include facilities construction on the NIH campus; at the NIH’s Rocky Mountain Laboratories in Hamilton, MT; and at Frederick, MD.

**Severe Acute Respiratory Syndrome (SARS).** The recent outbreak of SARS reminds us that emerging and reemerging infectious diseases are a constant threat to national and global public health and security. Because of our long-standing commitment to infectious disease research, NIH was well-equipped to respond quickly to the SARS outbreak. Within weeks of the first SARS reports, NIH researchers working closely with colleagues at the CDC identified the coronavirus that causes SARS and developed new diagnostic tests. More recently, NIH forged innovative partnerships with industry and non-profit researchers to accelerate SARS vaccine development efforts and create and freely distribute a new SARS DNA chip. The SARS DNA chip is a powerful tool that will enable researchers to identify dangerous strains of the virus, track its spread, and develop targeted antiviral drugs. NIH will continue to collaborate with the CDC, FDA, and other agencies to accelerate and expand our research to improve the diagnosis, prevention, and treatment of SARS.

**HIV/AIDS.** More than 40 million people worldwide are living with HIV/AIDS, which has surpassed tuberculosis and malaria as the leading infectious cause of death, and another 30 million already have died from this dreaded disease. The central priority in addressing the global HIV/AIDS pandemic is development of a vaccine that is simple to administer, inexpensive, and induces long-lasting immunity. NIH currently is conducting phase 1 clinical trials of a novel vaccine that targets the three HIV subtypes that together cause most of the HIV infections around
the world. At least 10 new candidate vaccines and several new combinations of products will enter clinical trials in the next 2 years. Also, NIH will continue to establish and enhance the international research and training infrastructure, which is an important component of the effort to develop a vaccine and test other preventives and treatments.

**West Nile Virus.** CDC statistics indicate that cases of West Nile virus in 2003 are quickly outpacing those reported for the same period in 2002. NIH is testing, in phase I/II clinical trials, an innovative new treatment for West Nile. Also, NIH researchers have created a promising vaccine against the virus that protects monkeys from infection; human clinical trials will begin soon.

Other NIH efforts to control infectious diseases worldwide include new and expanded initiatives to support international malaria research collaborations, tuberculosis vaccine testing, hepatitis C research centers, and the development of new microbicides and other strategies to combat growing antimicrobial resistance.

**Genetics and Genomics.** With the sequencing of the human genome, scientists are focused on identifying genes involved in health and disease, characterizing genetic variation, and translating these discoveries into diagnostics, prevention strategies, and treatments.

The completed human sequence and related genomic resources accelerated the rate of discovery of genes underlying a range of important diseases and disorders. In fiscal year 2003 alone, genes were discovered that affect the ability to learn and remember, increase susceptibility to inflammatory bowel disease and prostate cancer, cause premature aging, influence alcohol consumption, and predispose certain individuals to depression following major life stresses. These discoveries will allow for the development of diagnostics to identify individuals at risk for these disorders, will facilitate the creation of animal disease models for detailed study of pathogenic mechanisms, and will guide potential therapeutic approaches.

The NIH is also collaborating with international scientists to identify genetic variations in different populations from around the world. This effort aims to identify genomic variations that predispose individuals to common complex disorders such as cardiovascular disease and adult onset diabetes. Such knowledge holds out the promise that physicians will be able to identify individuals at risk for specific diseases in their offices. These tools will allow doctors to employ pre-symptomatic preventive measures and treatments. At the same time, it is expected that knowledge of genetic variation will be used to predict the effectiveness and possible adverse effects of drugs and vaccines on the individual patient. Today, information on genes that encode drug metabolizing enzymes is already beginning the move toward the practice of “personalized medicine,” where specific drugs are selected for optimal efficacy in each patient. As medicine of the future continues to benefit from publicly funded research, our citizens will lead longer, healthier, and higher quality lives.
The public investment in research yields a vast array of scientific advances every year. The select few highlighted below represent the development of new and improved treatments, diagnostics, or prevention strategies that will have an impact on public health, or the accrual of fundamental knowledge critical to the discovery process that holds the promise of leading to innovative and/or life-saving healthcare interventions.

**Improved Long-Term Treatment for Breast Cancer Survivors.** In a study that will change clinical practice and give postmenopausal women improved hope for a future without cancer, an international team of researchers found that postmenopausal survivors of early-stage breast cancer who took the drug letrozole after completing an initial five years of tamoxifen therapy had a significantly reduced risk of cancer recurrence compared to women taking a placebo. While tamoxifen is widely used to prevent breast cancer recurrence, it stops being effective after five years because, researchers believe, tumors become resistant to it. Taking letrozole after tamoxifen reduced the risk of recurrence by 43 percent—a result so dramatic that researchers stopped the study early so that all 5000 women participating in the study could begin taking letrozole.

**Dual Mechanism of Action of Type 2 Diabetes Drug Candidate.** More than 17 million Americans have type 2 diabetes, the most common form of the disease. The total economic cost of diabetes in the United States is more than $130 billion each year, and the incidence of type 2 diabetes is increasing dramatically, particularly among children. Type 2 diabetes patients are impaired both in their ability to produce and respond to insulin, which regulates our blood sugar (glucose) levels. Previous research by NIH-supported scientists has shown that mutations that impair the function of the protein glucokinase (GK) causes a rare form of type 2 diabetes called “Maturity-Onset Diabetes of the Young.” GK regulates the sensitivity of insulin-secreting pancreatic cells to glucose and regulates release of glucose by the liver. Based on this research, scientists hypothesized that a drug that activates GK would help restore normal glucose levels in type 2 diabetes. Working toward this goal, they screened 120,000 drugs and identified a single one that activated GK. This drug dramatically and effectively restored normal glucose levels in diabetic mice. Importantly, the drug achieved this by a dual mechanism: it stimulated insulin production by pancreatic cells and inhibited glucose production by the liver. This is the first identified drug to have an effect on both insulin production and insulin action—two processes that are impaired in type 2 diabetes. This study is a key example of how the NIH investment in basic research enabled researchers to identify a potential therapeutic agent for type 2 diabetes.

**Women's Early Warning Signs of Heart Attack.** Armed with the new knowledge from a recent NIH-funded study on early warning signs of heart attack in women, clinicians will now be able to recognize heart attack signs in female patients and take steps to prevent the attack and/or delay its complications. Although it is well known that one of the classic signs of a heart attack is crushing chest pain that radiates to the left arm and/or jaw, a recent NIH-funded study found that women and men have dramatically different signs and symptoms before and soon after a heart attack. Of 500 women who had been discharged from hospitals with a diagnosis of heart attack, nearly 95
percent said they knew they had new or different symptoms in the month prior to their heart attack. Importantly, only 30 percent of the women reported chest pain, and more than 40 percent did not even experience chest pain during the heart attack. Instead, the most frequently reported symptoms were unusual fatigue (70 percent of the women), sleep disturbance (48 percent) and shortness of breath (42 percent). These women delayed seeking treatment because they did not know the symptoms associated with heart attacks in women.

**Drug Reduces Risk for Prostate Cancer.** NIH-funded researchers presented the first-ever findings that prostate cancer can be prevented or delayed by a drug treatment. The drug, finasteride, inhibits the body's production of highly potent androgens, male hormones known to influence the development of prostate cancer. In June 2003, a 10-year trial involving nearly 19,000 participants nationwide was ended a year early due to the conclusiveness of the data. Men who took finasteride for 7 years were 25 percent less likely to develop prostate cancer than men taking a placebo. The drug's ability to prevent the disease was not dependent upon age, prostate specific antigen (PSA) level at enrollment, family history of prostate cancer, or race/ethnicity. While the results of this study are encouraging, there is a cautionary note. In the finasteride group, 6.4 percent of patients developed high-grade tumors versus 5.1 percent in the placebo group. While further study of finasteride is needed, these findings are a promising step in the effort to prevent and control the most common cancer among men in the United States.

**Development of Novel Immunosuppressant Drug.** NIH-supported researchers working with private sector scientists report the development of a potential new drug for specific and safe immune suppression following organ transplants as well as for the treatment of autoimmune diseases. Immunosuppressants are essential drugs given to prevent transplant rejection and to treat autoimmune diseases such as lupus and rheumatoid arthritis. Currently used drugs have toxic side effects, including dangerous increases in cholesterol, blood sugar, and blood pressure. Researchers developed and studied a new drug, which specifically inhibits a critical protein in the immune system called Jak3. In mice with heart transplants and monkeys with kidney transplants, animals treated with this new drug survived much longer than untreated animals. Importantly, none of the side effects associated with the currently used immunosuppressants was observed. This drug is the first Jak3 inhibitor to show positive results in primates and further studies are being conducted in preparation for testing in humans.

**Fast-Acting Experimental Ebola Vaccine.** NIH researchers, in collaboration with colleagues from the Army Medical Research Institute of Infectious Diseases, developed a vaccine that completely protects monkeys from the Ebola virus after a single injection. Ebola – a deadly virus with the potential for use as an agent of bioterrorism – kills up to 90 percent of infected humans. If proven effective in human trials, this vaccine may one day allow scientists to contain Ebola outbreaks quickly by vaccination. This research also has enormous health implications because the same “prime-boost” approach used for this Ebola vaccine might be applied to other highly lethal viruses, such as the Marburg and Lassa fever viruses, as well as the SARS coronavirus.
Simple Assessment of Heart Disease Risk. NIH-funded researchers discovered a simple way to assess heart disease risk. In a study involving 45 healthy men aged 21 and older, some of whom have standard heart disease risk factors (age, family history, smoking, blood pressure, cholesterol, obesity/diabetes, etc.), researchers were able to link heart disease risk to the amount of a special type of cell in blood – endothelial progenitor cells. Those with fewer endothelial progenitor cells were at higher risk for heart disease. These special cells, generated in the bone marrow, carry out a critical function for the heart by repairing damaged blood vessel walls. The study also showed that blood vessels were much less likely to function – dilate and relax – appropriately in persons with low levels of these cells. These results, if confirmed in larger population studies, would give physicians a simple, but effective way to assess heart disease risk accurately for all patients.

How Hepatitis C Virus Persists. Persistent hepatitis C virus infection is a major cause of liver disease worldwide and is the leading reason for liver transplant in the U.S. NIH-funded researchers discovered that the virus persists in the body by thwarting the immune system’s efforts to eliminate it. As the virus begins to replicate in its human host, it manufactures a molecule which switches off a critical component of the immune system. It also prevents a key immune molecule from orchestrating a range of antiviral responses. When researchers blocked the ability of the virus to turn off the immune system, the restored immune system was able to reduce viral loads to nearly undetectable levels within days. This knowledge opens the door to the development of new therapeutic approaches for those who suffer from liver disease.

Anthrax DNA Decoded. The DNA composition of the deadly anthrax microbe, *Bacillus anthracis*, has been fully mapped by NIH-supported scientists. Researchers found a number of genes which play a crucial role in the bacterium’s ability to enter its host’s cells. For example, *B. anthracis* has the capacity to scavenge iron – present in the majority of host organisms – to enhance its survival in its host. This type of genetic information is invaluable to identifying new drug targets to fight against this dangerous pathogen.

Making Headway on Antibiotic Resistance. Understanding how bacteria develop drug resistance is crucial to controlling infectious diseases. In a recent study of tuberculosis, NIH-funded researchers pinpointed a specific gene that allows the tuberculosis bacterium to mutate its DNA and, as a result, to develop resistance against commonly used antibiotics. The role of the gene was further illuminated in mouse studies – mice infected by the bacterium lacking the gene did not develop resistance and responded to common antibiotics. On the other hand, mice infected with the normal strain of tuberculosis bacterium died quickly, even when treated with common antibiotics. In another NIH-supported study, researchers found that a single gene mutation was the source for the resistance of the malaria-causing parasite, *Plasmodium falciparum*, against the anti-malarial drug, chloroquine. Interestingly, the presence of this mutated gene also makes *P. falciparum* more susceptible to two other anti-malarial drugs, artemisinin and quinine. Overall, these discoveries related to drug-resistance in tuberculosis and malaria give scientists new ways to identify and attack the causes of these infectious diseases.
Researchers discover how embryo attaches to the uterus. Investigators, using biopsies of uterus linings, have determined how a human embryo initially attaches to the wall of the uterus – one of the earliest steps needed to establish a successful pregnancy. At about 6 days of age, the spherical embryo is coated with a protein, which allows it to roll along the uterine wall, sticking to the carbohydrates attached to the uterine wall. Gradually the rolling embryo slows to a complete stop. Cellular projections from the embryo then extend into the uterine wall and establish the blood supply to the developing embryo. This discovery may provide insights into infertility and early pregnancy loss, especially those that result from failure of the embryo to attach to the uterine wall. Findings may also offer insight into preeclampsia, a condition in which pregnant women develop dangerously high blood pressure that can lead to convulsions and even death. Preeclampsia appears to result from the failure to establish the blood vessels connecting the embryo to the maternal blood supply.

New drug slows functional decline in Parkinson’s disease. Findings from the first clinical trial of a compound known as coenzyme Q10 indicate that it can slow disease progression in early-stage Parkinson’s patients by improving the production of energy in the cell. Q10 levels and energy production are reduced in the cells of Parkinson’s patients. In addition, animal studies showed that this enzyme can protect the area of the brain that is damaged in Parkinson’s disease. If larger clinical studies now underway confirm this initial result, Q10 may ultimately provide a new way of treating Parkinson’s disease.

Structure of HIV-Neutralizing Antibody Solved. A team of scientists has solved the structure of an antibody that is able to neutralize the AIDS virus, HIV. The antibody, called 2G12, was isolated 10 years ago from one of the rare HIV-positive individuals who never developed AIDS. The structure helped to determine that the target of the antibody was two sugars on the HIV particle that are made by human cells. This finding explains that the vast majority of infected people do not make this antibody because the human-produced sugars are perceived as self by the immune system, and therefore, 2G12 is never produced. The structure of the antibody now provides scientists with a template for designing a vaccine with the capacity to stimulate the production of 2G12 which could neutralize HIV in all infected individuals.

New Neurons on Demand. Researchers discovered that a common signaling molecule, nitric oxide (NO), turns off the production of new neurons from neural stem cells in the adult brain. Using rats, the research team injected an inhibitor of NO production into areas of the brain where neural stem cells are known to divide. Remarkably, the number of neural stem cells that developed into neurons increased by 70 percent. By developing treatments that shut down the NO “off switch,” doctors may one day be able to generate new neurons in the brains of patients with traumatic brain injury and neurological disorders, including Parkinson’s and Alzheimer’s disease.

Genetic Risk Factor for Depression Uncovered. Depression is among the top five leading causes of disability and disease burden throughout the world. A long-sought research goal has been to understand why stressful life experiences can lead to depression in some people but not in others. A recent epidemiological study by NIH-funded researchers revealed that people with the “short” version of the serotonin transporter gene (5-HTT) have a much higher risk of depression than those with the
“long” version of the same gene. This study provides clear evidence of a gene-environment interaction, in which a person’s response to environmental changes is moderated by his or her genetic makeup.

**Finding the Cause of SARS. Identifying a Novel but Deadly New Human Coronavirus.**
In early 2003, the world became aware of an outbreak of a newly recognized, highly lethal pneumonia that was named severe acute respiratory syndrome (SARS). The outbreak is thought to have originated in southeastern China’s Guangdong province in November 2002, with subsequent spread to numerous other countries. NIH-supported investigators were the first to report the isolation of a virus that was conclusively linked to SARS patients. To identify the agent that causes SARS, clinical specimens were obtained from 50 Hong Kong patients with fever, cough, shortness of breath, pneumonia, and a history of close contact to another SARS patient. The researchers isolated an unknown virus from two of the patients and identified it as a new strain of coronavirus, which is normally a major cause of the common cold; evidence of infection with this particular coronavirus was subsequently demonstrated in 45 of the 50 patients. This identification of the coronavirus that causes SARS demonstrates that NIH is prepared to respond quickly to emerging disease threats and will help scientists worldwide to develop effective vaccines, drugs, and improved diagnostic tests to counter the further spread of SARS.

**Antimicrobial Agents Found in Human Milk.** About 10 million children under the age of five die throughout the world each year because of severe diarrhea and dehydration. The most common cause of this diarrhea is infection with the bacteria, *Campylobacter jejuni*. To infect a child, the bacteria must go through a series of steps, the first of which is to bind to the intestinal wall. NIH-supported researchers discovered that a long-chain sugar molecule in human breast milk blocked *C. jejuni* from infecting the intestinal cells, and infants receiving high levels of breast milk were protected against diarrheal infections. This discovery helps to explain why breast-feeding provides a safe, inexpensive and effective way of reducing the likelihood of diarrheal infections in babies and very young children and is especially important to consider when formulating public policy concerning infant feeding in non-hygienic environments. Equally important, this work introduces a promising new class of antimicrobial agents that could be developed for preventing and treating bacterial infections and are unlikely to induce bacterial resistance.

**Prevention of Premature Birth in Women at High Risk.** In the first large-scale trial of progesterone in women at risk of giving pre-term birth, scientists report that the experimental treatment with a form of progesterone called 17 P, enabled significant numbers of both Black and White women in the study to carry their babies to term. Pre-term delivery is the major cause of infant mortality and morbidity in the U.S. and contributes substantially to racial/ethnic health disparities. In addition, these infants also had lower rates of life-threatening complications of prematurity, such as a deadly inflammation of the intestine and colon. Further studies could determine whether 17P prevents pre-term delivery in women with other risk-factors for pre-term birth (such as twin or triplet pregnancies) and whether other progestin-related compounds might be equally effective, and easier to administer.
Non-Addictive Relief for Chronic Pain. Chronic neuropathic pain affects approximately 1 percent of the population, taking an enormous economic and social toll and producing unnecessary suffering in afflicted individuals. Current therapeutic options for chronic pain face adverse side effects and the potential for abuse and addiction. Basic research on the mechanisms of marijuana's effects on the brain led to the discovery of cannabinoid receptors. One type of cannabinoid receptor (CB2) is found almost exclusively outside of the brain and central nervous system, mostly in areas associated with immune function. To avoid any effects on the brain, NIH-supported researchers designed a drug to affect CB2 selectively. In both mice and rats, the new drug reduced pain sensitivity to two distinct types of pain, suggesting that the compound may have applications for treating pain of varying causes. This work opens up a new approach for the treatment of neuropathic pain, a disabling condition affecting millions of people within the United States alone. Furthermore, the development of pain medications that lack addictive liability should help diminish our Nation's growing problem of prescription drug misuse and abuse.

Gene Replacement Therapy for Deafness. The sensory hair cells of the inner ear play an important role in detecting sound, and people who lose hair cells due to diseases, infections, or accidents often lose some or all of their ability to hear. Many forms of inherited deafness are also due to abnormal hair cells. In the past, it was thought that only birds and reptiles were capable of generating new hair cells. Now, NIH-supported scientists have discovered a way to use gene therapy to generate new hair cells in the ears of adult mammals. Scientists used a virus to transfer a gene called Math1 into the ears of guinea pigs. Cells infected by the virus that do not normally make Math1, became hair cells. In addition, these new hair cells attracted fibers of the auditory nerve, suggesting that the new cells may be able to establish a link with the part of the brain that interprets sound. If this work can be duplicated in human beings, it may one day enable scientists to use gene therapy to enable deaf individuals to hear or to restore hearing to those who have lost it.

Stories of Discovery

Described earlier in this document are but a few examples of the many scientific advances achieved by NIH-funded researchers. Some represent years of research in the laboratory and the clinic, culminating in a new treatment or prevention strategy. Other advances reflect significant new knowledge about the fundamental processes in the cell or in the organs or systems that play a role in disease—these advances are still on the path to clinical application. Included below are two “stories of discovery” which we hope will more clearly articulate the many and varied scientific paths that lead from the idea to the clinic.
Story of Discovery
Gene Silencing Tool Leads to New Understanding of Health and Disease

It is not every day that scientists uncover nature’s deepest secrets, the ones that promise to change significantly our understanding of the biology of living things. The discovery of a simple way to turn off genes—gene silencing by RNA interference (RNAi)—is this kind of breakthrough. RNAi is a unique natural cellular system that researchers are now using to reveal the function of genes in animals, plants, and humans. RNAi also offers a promising new approach to treating AIDS and a host of other diseases. Heralding the importance of RNAi, Science magazine declared advances in this field to be the top scientific achievement of 2002.

Researchers believe that RNAi’s natural role is to modulate the activity of genes, reducing their expression for purposes of growth and/or self-defense. When viruses infect cells, for example, they direct the infected cell to produce specialized RNAs to help the virus survive. Researchers believe that RNAi is an ancient mechanism used to wipe away such unwanted, extra RNA, and some scientists speculate that it may even play a role in immunity.

Unexpected Discovery

The story begins with a simple experiment that, intriguingly, produced results directly opposite to what was expected. Scientists studying the genetics of plant growth noticed a curious result. The researchers were attempting to deliver an extra “purple” gene to petunias, but the flowers instead bloomed stark white. The result evaded genetic logic and fascinated biomedical researchers, who yearned to understand how adding genetic material could somehow silence an inherited trait. The mystery remained until, a few years later, two geneticists identified a similar process in animals. They discovered RNAi, which, operates like a molecular “mute button” to quiet individual genes.

The researchers had been using a molecular tool called antisense RNA to dampen gene activity in roundworms and tease apart genetic factors that contribute to cell growth and tissue formation. In this technique, scientists cause the normally single-stranded RNA to bind to an opposite, or “anti-,” strand. This blocks the RNA from delivering the instructions to make a protein. To their surprise, the researchers discovered that the activity of their laboratory preparation did not depend on the antisense RNA itself, but instead on a contaminant that was produced during the synthesis of the antisense RNA. The contaminant, it turns out, was a molecule of double-stranded RNA, which they called RNAi. The scientists quickly learned that they could turn off specific genes simply by feeding their experimental worms double-stranded RNA with the same sequence as the gene they wished to mute.
RNAi All Around

RNAi took the research world by storm. One scientist completely retooled his lab when he learned that RNAi could be used as a tool in fruit flies as well as worms. Using this popular insect model system, he uncovered a link between RNAi and Fragile X syndrome, which is the most common inherited form of mental retardation. Another researcher led a team that discovered RNAi’s pivotal role in the normal functioning of yeast cells, which share many features with the cells of humans. This discovery showed that the molecules that normally carry out RNAi also help to organize chromosomes so they can be pulled apart during cell division, the key process that allows cells to replicate.

Scientists investigating gene function began to try RNAi in other organisms and found that the technique could be applied nearly universally to manipulate gene activity. One research group devised a way to use RNAi to silence individually each and every gene in an organism. Using this genome-wide screen to study energy balance in *C. elegans* (the common round worm), they found 335 genes that, when turned off, lead to a thinner worm. Silencing 112 genes led to a fatter worm. Because many of these genes also are found in humans, this RNAi-based research may have important implications for understanding and treating obesity.

RNAi to the Rescue

Researchers predict that in addition to RNAi’s potential for solving many of the mysteries encoded in our genes, the technique holds promise for new therapies. Several scientists have crafted clever tools for getting living cells to produce specific forms of RNAi. These methods have greatly enhanced researchers’ ability to explore RNAi’s medical promise in mammalian cells. For example, in recent lab tests with isolated cells, researchers have succeeded in using RNAi to kill HIV, the virus that causes AIDS. Biologists are now working hard on the very challenging problem of developing ways to deliver RNAi to the body in order to make RNAi a practical means for treating, and perhaps preventing, disease.
The development of nuclear magnetic resonance imaging (MRI) has revolutionized the practice of medicine. MRI has been used successfully for over 15 years to generate images of soft tissue in the human body. The technique is the diagnostic method of choice for many diseases, has eliminated the need for much exploratory surgery, and can provide critical guidance for surgical intervention. Today, more than 60 million of these non-invasive procedures are performed worldwide each year.

The story of MRI begins more than half a century ago, in 1946, when nuclear magnetic resonance (NMR) was discovered by Felix Bloch and Edward Purcell. Bloch and Purcell found that when certain nuclei are placed in front of a large magnet, they absorb radio-frequency energy and this energy is re-emitted when the nuclei relax back to their original state. With this discovery, the NMR spectroscopy became an important method for the analysis of chemical compounds. Bloch and Purcell won the 1952 Nobel Prize for Physics for their discovery.

Building on the discoveries of Bloch and Purcell, Paul Lauterbur described nuclear magnetic resonance imaging (MRI) in 1973. Lauterbur, who has been an NIH grantee since 1972, discovered that using a graduated magnetic field (a magnetic field that is slightly stronger, or weaker at each point on the item being visualized), produces enough contrast in the subsequently emitted radio waves to allow creation of a two-dimensional image. Sir Peter Mansfield laid the basis for transforming Lauterbur’s discovery into a practical technique by applying a mathematical method that rapidly analyzed the radio signals to assemble a three-dimensional image. In 1977, the first MRI exam was performed on a human being and, in 2003, Drs. Lauterbur and Mansfield received the Nobel Prize in Physiology or Medicine for their development of these imaging technologies.

The first MRI procedure was long and complicated, taking over five hours to produce a single, coarse image. Substantial advances now allow physicians to have clear images in seconds and MRI is a routine diagnostic method. The most frequent uses of MRI are for detailed imaging of the brain and spinal cord, but it is used to examine almost all organs of the body and has become an important adjunct to treatment.

Many adaptations and improvements have been and continue to be made in MRI, broadening its use in medical care and, in fact, extending the boundaries of care. One such adaptation is functional magnetic resonance imaging (fMRI), a relatively new technique developed by NIH-funded scientists to measure the quick and minute metabolic changes that take place in the active brain. fMRI studies can provide both an anatomical image and a minute-to-minute record of brain activity. In the health care arena, fMRI has a multitude of uses including detecting abnormalities hidden from other imaging methods by bone, monitoring the development of brain tumors in order to intervene more effectively, and diagnosing strokes at a very early stage so that treatment can be initiated sooner.

To date, the most popular fMRI technique utilizes blood oxygenation level dependent (BOLD) contrast, which is based on the differing magnetic properties of oxygenated and deoxygenated blood. These magnetic susceptibility differences lead to small, but detectable, changes in image intensity. Unfortunately, head movement and physiological sources of variability often hinder detection of signal changes. NIH investigators recently introduced a new method for removing the artifacts of movement variability by using a motion sensor system combined with adaptive noise filtering techniques. This computerized filtering approach is a “real-time” tool used for continuous monitoring of fMRI during clinical and cognitive research studies.
Functional MRI is being used extensively to study language processing and functioning because it can determine exactly which part(s) of the brain is responsible for crucial functions such as thought, speech, movement, and sensation. Studies are determining whether the patterns of brain activity observed during language processing can be useful diagnostically or in monitoring educational or therapeutic interventions.

Functional MRI also is providing a tremendous opportunity for the study and treatment of epilepsy. NIH researchers are integrating information on the suspected location of a brain seizure with information about surrounding brain function in order to improve outcomes of surgical procedures used to alleviate brain seizures.

An important arena for MRI is image-guided intervention. NIH researchers have designed and developed a system, used in numerous neurosurgical procedures, that integrates image analysis and visualization. The system enhances and accelerates tissue characterization and the precise localization of targets such as brain tumors.

Improving and expanding MRI technology continues at NIH, as researchers explore new ways to use this non-invasive imaging method to obtain quick and accurate diagnoses and to treat diseases and injuries more effectively.

**Management Innovations**

To further NIH’s scientific agenda, the agency’s management and administration must be effective and efficient. From the introduction of new information technology and business systems, to the streamlining of governance structures and the development of a new approach to portfolio management, continual improvement of management and administrative functions is at the forefront of NIH agency priorities. A few highlights of these efforts are described below.

*Improved and Integrated Business Systems.* NIH is making rapid progress to modernize its business and financial systems. An agency-wide information technology system, known as the New Business System (NBS), is integrating processes such as acquisitions, travel, property, and financial management reducing the cost and complexity of doing business, increasing service levels, and improving management controls. NBS serves as a proof of concept for, and a major element of, the DHHS Unified Financial Management System. As both systems mature, the NBS will merge into the single financial management system envisioned by DHHS.
**A More Nimble Agency Leadership**

**Structure.** As the NIH has grown in size and complexity, there has been an increased focus on a more efficient means of trans-NIH coordination. To create a more agile means by which the Agency makes administrative management decisions, the NIH Director formed the NIH Steering Committee. The committee is chaired by the NIH Director and made up of a rotating membership of 10 Directors representing the 27 NIH Institutes and Centers (ICs). While the NIH Director and IC Directors will continue to formulate their specific scientific directions and priorities as well as operational oversight of their respective institutes and centers, the Steering Committee will focus on NIH-wide policies and important operational decisions.

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The NIH budget doubled in the five years from FY 1999 through FY 2003. The agency entered the post doubling period far stronger and better positioned to improve health through advances in research. New insights into human biology and behavior are bringing us closer to prevention strategies and treatments for many of the most dreaded diseases and conditions. The NIH portfolio is broader and deeper making us better prepared to handle unexpected health crises; and NIH systems of management and administration are being strengthened to better serve the public and medical science. The trust and responsibility placed in NIH will be honored and met with innovations that lead to substantive improvements in health.

### Story of Management Innovation:

**Peer Review and Electronic Grants Administration**

The NIH peer review system is recognized as the cornerstone underpinning the remarkable progress in biomedical discovery and innovation. The NIH Center for Scientific Review (CSR) is the focal point of the peer review system at NIH. It reviews approximately 70 percent of the grant applications submitted to NIH, while other applications are reviewed by the Institutes and Centers. In fiscal year 2003, a record-breaking 66,000 grant applications were received by CSR.

The recent rapid pace of discovery has dramatically changed the landscape of biomedical research. NIH has taken steps to ensure that its peer review structure remains responsive to present and future needs, while improving efficiencies to better manage the increased workload. CSR uses the service of over 11,000 scientists each year to serve on peer review panels that evaluate grant applications. In a process guided by teams of leading experts in each relevant field and extensive comment from stakeholders, CSR is in the final stages of crafting new and more flexible review panels organized into 24 scientifically-related clusters.

With the initial phase of the reorganization nearly complete, CSR is now focused on implementation and will finish the process in 2004.

Concurrent with this reorganization and in step with the e-government initiative in the President’s Management Agenda, NIH has incorporated new technologies into the review process. An important component of the Federal “Grants.gov” initiative (a one-stop portal for the Federal electronic grants administration), electronic Research Administration (eRA) aims to implement end-to-end electronic grants administration for a wide range of NIH research award mechanisms. eRA eventually will encompass logistics for the review of applications, award notification, and financial and technical reporting. The benefits—both to grantees, NIH, and other HHS agencies—of migrating to eRA are huge. There will be an improvement in data quality and significant savings in paper, space, effort, and time. And, combined with other changes in grants administration, including the use of a web-based system that allows peer reviewers to share their critiques before the actual peer review meeting, the waiting period from submission of an application to a grant award is expected to shorten by more than two months, from 9/10 months to 7 months. These initiatives will result in greater efficiency and effectiveness in funding the most meritorious research projects.
Building upon ongoing interactions with scientists and administrators in the Department, NIH’s participation in the Department's Research Coordination Council (RCC) provides a valuable venue to identify additional opportunities for enhanced coordination and collaboration in research and related dissemination efforts. The NIH Roadmap, a major initiative for the agency, was presented to the RCC last year. There have been followup meetings with programmatic and policy officials in other agencies within the Department, and these are likely to yield additional collaborative efforts.

### National Institutes of Health
**RD&E Funding by Research Theme**
**Competing Requests for Grant Applications and Requests for Proposals for R&D Contracts**
**FY 2005 President's Budget**
(Dollars in Thousands)

<table>
<thead>
<tr>
<th>Research Theme</th>
<th>Competing RFAs and RFPs for R&amp;D contracts 2/</th>
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<tbody>
<tr>
<td>I. Working Toward Independence</td>
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<tr>
<td>II. Rallying the Armies of Compassion</td>
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</tr>
<tr>
<td>III. No Child Left Behind</td>
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<tr>
<td>IV. Promoting Active Aging and Improving Long-Term Care</td>
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</tr>
<tr>
<td>V. Protecting and Empowering Specific Populations</td>
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<td>VI. Helping the Uninsured and Increasing Access to Health Insurance</td>
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<tr>
<td>VII. Realizing the Possibilities of 21st Century Health Care</td>
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<tr>
<td>VIII. Ensuring our Homeland is Prepared to Respond to Health Emergencies</td>
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<tr>
<td>IX. Understanding Health Differences and Disparities---Closing the Gaps</td>
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<tr>
<td>X. Preventing Disease, Illness, and Injury</td>
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<td>XI. Agency-Specific Priorities (all other progs. 1/)</td>
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<td><strong>Total Budget Request</strong></td>
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</tbody>
</table>

1/ Other Programs - Includes grants, intramural, other R&D contracts, RMS
2/ Includes $150M for Type I Diabetes

Support for categories I-X is also accomplished through investigator-initiated research, the most prevalent mechanism NIH uses to support research. Through agreement with the Office of the Assistant Secretary for Planning and Evaluation, these investigator-initiated activities are not included in categories I-X.
FY 2005 BUDGET POLICY

The FY 2005 program level for the NIH is $28,805 million, an increase of $764 million or 2.7 percent over the FY 2004 Enacted Level. The NIH’s President’s Budget authority request to the Labor/Health and Human Services/Education Appropriations Subcommittee is $28,527 million. The budget authority request to the Veteran’s Administration/House and Urban Development Appropriations Subcommittee is $80.5 million for the NIEHS Superfund research program. The NIH program level also includes $150 million for the Type I Diabetes Initiative appropriated by Public Law 107-360. Of this program total, $47.4 million is included in the budget authority request of the Public Health and Social Services Emergency Fund (PHSSEF), for research in radiological/nuclear countermeasures.

NIH Roadmap for Biomedical Research

In FY 2005, NIH will direct $237 million towards the Roadmap initiatives discussed in the previous section; $60 million will be provided by the NIH Director’s Discretionary Fund (DDF), and the remaining $177 million will be provided by the Institutes and Centers (ICs). The IC contribution to support these trans-NIH research goals will represent 0.63 percent of each individual budget request for FY 2005.

The funding level for New Pathways to Discovery is $137 million, funding for Research Teams of the Future is $39 million, and funding for Re-engineering Clinical Research is $61 million. More detailed information on the funding levels for the NIH Roadmap is shown on pages 37-40.

Biodefense

The NIH FY 2005 Budget for biodefense research was built as an integral part of the NIH long-range strategic plan for biodefense research. NIH has already made substantial progress in implementing the long-range strategic plan for biodefense research as evidenced by the recently released progress report on biodefense research against Category A biological agents. Category A biological agents include: Bacillus anthracis (anthrax); Clostridium botulinum (botulism); Yersinia pestis (plague); Variola major (smallpox) and other pox viruses; Francisella tularensis (tularemia); and Viral hemorrhagic fevers, such as Ebola, Marburg, and Lassa fevers. This progress report can be found at (http://www.niaid.nih.gov/biodefense/research/category_A_Progress_Report.pdf).

Planned new and expanded initiatives in FY 2005 will include the following major milestones and activities:

- Complete the establishment of the extramural Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research (RCE) by awarding the last two
(of ten) (peer-reviewed) cooperative agreements. These centers will be based regionally and will form the heart of the extramural research activities in their geographical area. Each center will provide support to researchers by making available specialized equipment and tools, including the specialized laboratories required; providing specialized knowledge and expert advice; and conducting specialized training. In addition, each center will conduct and be recognized as national experts in specialized areas of biodefense research.

- Initiate the second phase of construction of specialized, biosafety research laboratories for extramural researchers. These specialized research laboratories, at the BSL-3 and -4 levels, are necessary to conduct research on the highly dangerous and infectious pathogens in the biodefense research field. The laboratories are a critical component of the planned network of extramural RCEs.
- Undertake the Phase I clinical trial of a plague vaccine candidate.
- Conduct an extended Phase II clinical trial of an advanced version of the Ebola vaccine candidate that is designed to work quickly, and to protect against multiple strains of Ebola.
- Conduct animal model testing of an Ebola vaccine candidate that is designed to also protect against other viral hemorrhagic fevers, such as Marburg and Lassa viruses.
- Conduct animal model testing of a vaccine candidate against tularemia and initiate a Phase I clinical trial.
- Initiate research and animal model testing of vaccine candidates against Rift Valley Fever.
- Facilitate collaborative partnerships between industry, academia and government research organizations to research and develop novel biodefense products through the launch of challenge or partnership grants.

Obesity

The epidemic of obesity threatens the Nation's health by sharply increasing the incidence of type 2 diabetes, fatty liver disease, kidney failure, cardiovascular and other diseases. However, dramatic advances in our understanding of regulation of appetite and weight offer new opportunities to develop methods to treat obesity and to prevent type 2 diabetes and other obesity-related diseases.

To coordinate and accelerate its obesity research efforts, NIH has created an Obesity Research Task Force. With the assistance of external scientific and public advisors, the Task Force is developing a strategic plan for NIH obesity research. The FY 2005 President's Budget includes $22 million for expanded trans-NIH research programs in obesity and diabetes, with the distribution following the priorities of the Obesity Task Force:
• Prevention and Treatment of Childhood Obesity in Primary Care Settings ($3.5 million) This NIH initiative will focus on developing effective, primary care office-based programs to prevent and/or treat childhood obesity. This effort will lead to the development and testing of programs to accomplish weight loss in overweight children and to prevent excessive weight gain in children at risk for overweight.

• Site-Specific Approaches to Prevention and Treatment of Pediatric Obesity ($3.5 million) This NIH initiative will solicit grant applications for the prevention or treatment of pediatric obesity in various site-specific settings (e.g., family/home, daycare or pre-school, school, or other appropriate community venues), and will complement the research effort in primary care settings.

• Neurobiological Basis of Obesity ($6.0 million) This NIH initiative will support collaborative programs focusing on understanding the biological basis of human eating behavior with a goal of developing better strategies for the prevention of obesity. A primary goal is to bridge the gap between understanding at the molecular and genetic level of neural pathways involved in food intake and the understanding of behavioral influences on human obesity.

• Bioengineering Approaches for Prevention and Treatment of Overweight and Obesity ($2.0 million) This NIH initiative will bring state-of-the-art bioengineering technology to address the range of practical problems in energy balance, intake, and expenditure that are associated with the epidemic of obesity in American adults and children. The goal is to provide technologies and tools to facilitate research and support behavioral change. Of particular interest will be new ways to achieve short- and long-term measurement of total energy intake, expenditure, exchange, and balance, e.g., resting and basal metabolic rate; physical activity under various physiologic conditions and activities, including work, sleep, and leisure activity.

• Obesity and the Built Environment Program ($1.0 million) This NIH initiative will seek to understand mechanisms by which the built environment (e.g., community design, planning, and development) influences obesity and related co-morbidities. It is critical to understand the impact of the built environment (urban/rural planning, housing structure, transportation issues, and the availability of public and green spaces) on mental health, physical activity, nutrition, and access to healthy foods. Modifying such parameters may reduce the prevalence of obesity in adults and children.

• Obesity Clinical Research Center (OCRC) ($6.0 million) This NIH initiative will use the wide-ranging expertise and sophisticated infrastructure/technology that are available in the Intramural Research Program (IRP), but not at most institutions that conduct clinical research. The Center will include a “magnet” approach, in which expertise and resources from across the IRP are focused on state-of-the-art clinical investigative strategies,
laboratory support, and imaging capabilities to pursue obesity research in a synergistic manner.

AIDS

Consistent with the development of the NIH nonBiodefense research budget, the AIDS research program would increase by 2.8 percent or $80 million, for a total of $2,930 million. A discussion of the Program Assessment Rating Tool (PART) used to evaluate the NIH AIDS Research Program may be found on page 22 of the Office of AIDS Research section of the Congressional Justification.

Mechanism Discussion

The funding of basic biomedical research through investigator-initiated research, including Research Project Grants (RPGs), and the support of new researchers with new ideas are the highest priorities for the National Institutes of Health. The FY 2005 request would support 10,393 competing RPGs, for $3,609 million, an increase of 258 competing RPGs over the FY 2004 Enacted Level estimate of 10,135 competing RPGs. This budget request will allow NIH to support nearly one-in-three applications for competing research project grants.
The FY 2005 President’s Budget provides an aggregate 1.3 percent increase in average cost for Research Project Grants, consistent with the Gross Domestic Product deflator. Within this 1.3 percent aggregate increase, NIH is providing average cost increases of 1.9 percent for direct recurring costs in noncompeting continuation awards; competing RPGs receive an average cost increase of 1 percent.

Research Centers increase by $152 million and 5.9 percent in the FY 2005 request. In FY 2005, NIAID plans to establish two additional Regional Centers of Excellence for Biodefense and Emerging Infections. These additional centers are estimated to cost $21 million in FY 2005.

The NIH will support an additional +225 Full-Time Training Positions (FTTPs) in FY 2005, for a total of 17,791 FTTPs. The increase of +225 FTTPs will support additional trainees in the Roadmap Interdisciplinary Research Training Initiative (+198 FTTPs) biodefense research (+22 FTTPs), and an expansion of +24 FTTPs in the recently established National Institute of Biomedical Imaging and Bioengineering, offset by a slight decrease (-19 FTTPs) in several ICs. Stipends for pre-doctoral and post-doctoral recipients of the Ruth L. Kirschstein National Research Service Awards will remain at FY 2004 levels. The total increase in Research Training is $15 million, or 2 percent.

Research and Development (R&D) contracts decrease by $111 million and 3.9 percent compared to the FY 2004 Enacted Level, due to the completion of one-time activities. NonBiodefense R&D contracts increase by $92 million, or 4.5 percent. This increase is offset by a decrease of $203 million in Biodefense R&D contracts—the procurement of the contract phase of the advanced development of the next generation anthrax and smallpox vaccines is completed in FY 2004, allowing these funds to cycle into other mechanisms of support in the Biodefense research program. Within the R&D contracts total of $2,706 million, $100 million is allocated for the Global Fund for HIV/AIDS, Tuberculosis and Malaria.

The Intramural Research program will increase by $106 million, or 4.0 percent. Within this increase, $34 million will support increased Biodefense research activities.

Research Management and Support will increase by $32 million, or 3.2 percent. With these funds, NIH will continue to manage its research portfolios and ensure appropriate stewardship of funds. Within this increase, $9 million will provide for increased scientific management and program oversight for biodefense activities.

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 2005, NIH is requesting a total of $150 million for extramural grants for these facilities.
In the FY 2005 request, B&F would be funded at $99.5 million. The FY 2004 and FY 2003 amounts are comparable for the transfer of $10 million in facilities costs previously funded by the Institutes and Centers, to more accurately reflect NIH-wide B&F allocations. The FY 2005 request will provide $5 million towards the design of the Animal Research Center. Studies in the NIH Master Plan document the need to plan for new replacement research facilities in the southeastern portion of the main campus on the site of the present day central animal facilities, which are outmoded, expensive to maintain, and inadequate to sustain modern animal research. Another $9.5 million will be used to build a replacement facility to improve the security buffer at Rocky Mountain Laboratories in Hamilton, Montana. This facility will replace existing buildings that are too close to the security perimeter of that campus. The remaining funds, will be used for repairs and improvements ($59.2 million), essential safety and regulatory compliance ($6.0 million), renovations ($10.8 million), equipment and systems ($7.0 million), and concept development studies ($2.0 million).

Included in the Buildings and Facilities mechanism of support is $8 million provided to the National Cancer Institute (NCI). As part of NIH’s ongoing review of its facilities program and management processes, it was determined that NCI should request specific authorization to undertake repairs and improvements at the NCI-Frederick campus operated as a Federally-funded Research and Development Contract (FFRDC). The request for this authority is included in the NCI budget request for FY 2005.

The Office of the Director (OD) increases by $33 million, or 10 percent. $60 million has been reserved in the NIH Director’s Discretionary Fund for allocation to Roadmap activities. Another $10 million is available in the DDF for non-Roadmap projects, making a total for the DDF $70 million in the FY 2005 request. The increase for the OD excluding Roadmap funding is $8 million or 2.7%.
Other Key Issues

Radiological and Nuclear Countermeasures

The use of a nuclear or radiological device in a terrorist attack presents a critical challenge to the United States. The most plausible terrorist radiological or nuclear scenarios envision situations that are more limited in scope and in which the health effects of radiation exposure could be mitigated by intensive medical intervention. However, it is also clear that little progress has been made during the last forty years to improve the medical management of injuries produced by radiation.

In FY 2005, NIH will therefore initiate a research effort that will focus on the development of three kinds of medical interventions:

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

The Department of Health and Human Services (HHS) has requested that $47.4 million be provided in FY 2005 to support specific targeted research activities needed to develop radiological and nuclear threat countermeasures. While NIH would manage and oversee this work, these funds are budgeted in the Public Health and Social Services Emergency Fund.
Placing these funds in the PHSSEF enables them to be appropriated in one place, as with some other biodefense funds in the DHHS, and then allocated to the proper NIH Institutes or Centers to implement the targeted activities.

**IT Projects**

Included within the overall budget amount is continued funding for four of the 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).

The Unified Financial Management System (UFMS) is being implemented to replace five legacy accounting systems currently used across the HHS Operating Divisions. 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 OPDIVs 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. The NIH budget request includes $4.923 million to support this effort in FY 2005.

**NIH Management**

NIH continues to make progress on its restructuring activities, including those in support of the DHHS “One Department” goals and the Presidential Management Agenda. Earlier this year, the NIH Director created an Administrative Restructuring Advisory Committee (ARAC) to review the following NIH administrative functions: Acquisition, Finance, Budget, Grants Management, Facilities, Equal Employment Opportunity, Information Technology and Human Resources. Sub-committees were established to review each separate function, and reported back to the ARAC. The ARAC report recommendations are in the process of being implemented, which will further improve the efficiency of NIH administrative operations.

The NIH has completed a risk assessment of its programs to identify the risk of improper payments. The NIH used an independent contractor to assess the risks, and based on that independent review, the NIH believes the risks of improper payments is negligible.

In FY 2003, more than 1,000 FTEs were placed under A-76 review— including extramural administrative support to program, review and grants management, and real property management. NIH won the Grants Administration competition and the Real Property Management competition. Plans are underway to implement the Most Effective Organization for these functions in the spring, 2004. Consistent with the Department’s commitment that
affected employees will have a job, NIH will be using all tools at its disposal to retrain, counsel, and place affected employees within NIH, DHHS, other Federal agencies or alternate employers.

The workforce at NIH is one of its greatest assets because of the large numbers of staff and their great diversity of qualifications, disciplines, types of appointments, and levels of expertise. This array of talent and systematic interdependence of scientific, programmatic, and administrative staff and missions has helped create NIH's success and its reputation as one of the world's leading biomedical research organizations. As the nature of science continues to change, the tools of administering that science must also change. NIH must ensure that it continues to meet these new opportunities with the best tools to attract and retain its staff, ensure the appropriate talent and skills, and plan for its future workforce needs. NIH will continue to oversee the staffing of personnel to manage the research portfolio, and recruit the best scientists to conduct world-class research. In FY 2005, NIH is requesting 17,522 FTEs, the same level as in FY 2004.

**FULL-TIME EQUIVALENTS (FTEs)**

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