Introduction
Statement of the Director, NIH

Reflection on the origins of NIH aptly frames assessment of the current state of biomedical and behavioral research. After World War I, scientists sought funding to establish an institute that would apply their rapidly growing knowledge of chemistry to the field of medicine. When no philanthropic money materialized, the visionary Senator from Louisiana, Joseph E. Ransdell, led Congress to pass a bill in 1930 that would transform the Nation's small Hygienic Laboratory into the "National Institute of Health" (singular). The change in title underscored a much more significant change—toward public support for medical research. This was a defining moment in the history of biomedical research and health care for our country and for the world. Years later, in 1945, the noted scientist and intellect Vannevar Bush recognized the importance of research to the Nation when he said that *"scientific progress is one essential key to our security as a Nation, to our better health, to more jobs, to a higher standard of living, and to our cultural progress."*

Transformation! The payoff of the investment in NIH

In the over 70 years since the Ransdell Act, NIH transformed modern research and medicine in countless ways—some well known, others so much a part of daily life that their scientific origin is forgotten. We made tremendous improvements in the recovery from heart disease and stroke. For patients with clogged arteries, NIH scientists developed a stent imbedded with the cancer drug Taxol®, which prevents scars from forming during its slow release. This revolutionary drug-device combination dramatically reduced artery reclosing rates to 3-6 percent and is expected to substantially reduce the number of open-heart bypass surgeries—previously the only alternative for some patients. What seems obvious today—for example, knowing about the importance of a healthy diet and the benefits of exercising—are the results of research studies pioneered by NIH. Pregnant women get the most detailed advice available about what foods to eat and what environmental exposures to avoid—again, the result of NIH research. In another example, prostheses known as cochlear implants now allow hearing-impaired children to hear and speak. Worldwide, nearly 100,000 individuals are fitted with cochlear implants, and, in the United States, roughly 22,000 adults and 15,000 children have them. NIH-supported scientists showed that profoundly deaf children who receive cochlear implants at an early age develop language skills at a rate comparable to children with normal hearing.

Our research breakthroughs extend to vision-impaired patients. Eight million older Americans are at high risk for advanced age-related macular degeneration (AMD), with 1.3 million developing AMD within 5 years if untreated. However, a large NIH-sponsored clinical trial established that a daily regimen of antioxidant vitamins and minerals delays the onset of advanced AMD by 25 percent. New drugs (Macugen and Lucentis) that block abnormal blood vessel growth, a hallmark of AMD, also are now available to stave off and, in some cases, reverse vision loss. We possess more effective drugs for treating diseases affecting bones and joints; for example, for patients with moderate to severe knee pain, injections of hyaluronic acid lubricate the damaged joint and may slow progression of disease. We developed new virus-like particle technology that formed the basis for new commercial vaccines that target specific cancers. In June 2006, the U.S. Food and Drug Administration approved the vaccine Gardasil, which is highly effective in preventing infections with the human papillomavirus types that cause the majority of cervical cancers. Worldwide use of this vaccine could save the lives of 200,000 women each year. We funded research that led to the discovery and development of antiretroviral therapies to treat people with HIV infection. As of today, antiretroviral therapies are the most effective means of treating HIV infections, resulting in improved quality of life and life expectancy for those with access to these drugs. A recent study indicates that highly active antiretroviral therapy has saved approximately 3 million years of life in the United States alone.

An important public health success story is the reduction in tobacco use and related diseases. In the last decade, overall cancer death rates dropped for the first time in a century, driven largely by the dramatic reduction in male smoking from 47 percent in the 1960s to less than 23 percent today. This success has been a trans-HHS victory, with

significant research investments over the last 50 years made by many Institutes and Centers.

These are just a few examples by which NIH research laid the foundation for modern medicine, generating enormously better health for the population worldwide. Partly as a result of research, the disability rate in our elderly population has declined by 30 percent since 1982.

NIH research also is a key driver for the private sector, as predicted by Vannevar Bush in 1945. As an example, between 1998 and 2004 alone, a total of 3,114 new technologies were brought to market by 185 universities, hospitals, and private research institutions. From 1980 to 2004, a total of 4,543 new companies were formed around technologies developed by research institutions, many of them directly funded by the NIH. NIH is, indeed, a tremendous asset for America.

Imagine! Where are we going?

We still have a long road in front of us. But thanks to a steady flow of basic research discoveries, NIH is well-positioned to find new treatment and prevention strategies for a host of our most debilitating diseases. These research breakthroughs of the future will more quickly feed into routine medical practice. The health care system itself will undergo a rapid change. It must, since the current trends—surging costs coupled with the rapid rise of chronic diseases such as obesity and diabetes, the increasing mental health needs in our modern society, the aging population, the emergence and reemergence of infectious diseases—are unsustainable. Science needs to tell us how to strike these diseases before they strike us.

Our goal at NIH is to provide the scientific evidence base that will usher in an era where medicine is ***predictive, personalized, preemptive, and participatory***. This will be a profound transformation from the current model of late-stage "curative" interventions, and one that this Nation must undergo in the coming decades if we are to succeed in providing access to care for all Americans at reasonable costs.

To reach this long-term goal, NIH is strategically investing in research to further our understanding of the fundamental causes of diseases at their earliest molecular stages so that we can reliably ***predict*** how and when disease will develop and in whom. Because we now know that individuals respond differently to environmental conditions according to their genetic endowment and their own behavioral responses, we can envision the ability to precisely target treatment or other interventions on a ***personalized*** basis. Ultimately, this individualized approach will allow us to ***preempt*** disease before it occurs, utilizing the ***participation*** of individuals, communities, and health care providers as early as possible in, and throughout, the natural cycle of a disease process. The discoveries we are making today are paving the way to make this future a reality.

Consider how more predictive and personalized treatments could improve the safety and effectiveness of medications. We know that drugs are not in the "one size fits all" category. The same medication can help one patient and be ineffective for, or even toxic to, another. With the emergence of a field of research called pharmacogenetics, we will be increasingly able to know which patients will likely benefit from treatment and which patients will not.

What are the roadblocks en route?

Major speed bumps confront NIH on the road to success. While we have made progress in discovering specific aspects of disease and generated numerous treatments that deliver desirable outcomes, large gaps remain in our fundamental understanding of health and disease. Disease and injury are constant threats to humankind. For example, military casualties suffering from blast injury pose an immediate challenge and highlight how the gaps in our knowledge on these and other traumatic brain injuries hinder medical researchers who are striving to optimize regenerative treatments. Infectious diseases remain among the leading causes of death worldwide. More than 30 newly recognized infectious diseases and syndromes emerged in the last two decades alone, including HIV/AIDS and

SARS. Infectious diseases that once seemed to be fading, such as tuberculosis and malaria, have resurged, and the emergence of antibiotic-resistant bacteria is making many common infections increasingly difficult to treat. There is concern that a new influenza virus will emerge with the capacity for sustained human-to-human transmission. Because the new strain would be unrecognized by the human immune system, it could lead to widespread infection, illness, and death, similar to what occurred in three such 20th century pandemics in 1918, 1957, and 1968.

The tragic events of September 11, 2001, and the deliberate release of anthrax spores in the Nation's capital drove home the realization that certain deadly pathogens, such as smallpox or anthrax, have the potential to be used deliberately as agents of bioterrorism against the civilian population. Similar potential exists for radiological, nuclear, and chemical threats.

To unravel the intricacies of the human body, we must find out what is happening at several levels—molecules, cells, organs—and how a dizzying number of interactions at each of these levels contribute to the health of the whole system. Efforts to prevent, detect, and treat disease require that we understand the complexity of the many biosystems of the human body. As the questions become more complex, and even as knowledge grows, science itself grows more multifaceted. We recognize that to effectively push science forward, researchers and scientists must begin to work more collaboratively to develop unifying principles that link apparently disparate diseases through common biological pathways and therapeutic approaches.

Today, and in the future, NIH research must reflect this new reality. Advanced technologies, including the sophisticated computational tools and burgeoning databases, likewise span diseases and disciplines. The scale and intricacy of today's biomedical research problems increasingly demand that scientists move beyond the borders of their own discipline and apply new organizational models for science. One of NIH's most pressing challenges is to generate and maintain the biomedical workforce necessary to tackle the converging research questions of this century.

Adding to the level of complexity, many of the public health problems NIH confronts have a behavioral component. To confront the escalation in obesity, for example, NIH must address a multitude of intersecting factors, from inherent biological traits that differ among individuals; to environmental and socioeconomic factors; to behavioral factors—which may have both molecular and environmental influences. The obstacles of today's obesity epidemic are daunting, yet the discoveries emanating from previous research investments offer unprecedented opportunities for new scientific research efforts to help meet these challenges.

Innovate! That's the path to a healthy state.

With the NIH Reform Act of 2006 (Pub. L. No. 109-482), Congress provided a statutory foundation for the centerpiece of the NIH Roadmap for Medical Research—a Common Fund that provides “incubator space” to spur innovation. The Common Fund supplies a centralized source of funding for trans-NIH initiatives to meet the research and training needs of the 21st century and stimulate innovation. To garner support from the Common Fund, research initiatives must not only be trans-NIH and fill a gap in our knowledge base, but also be potentially transformative. The Human Microbiome project, launched in 2007, is one such initiative, promising to reveal how bacteria and other microorganisms that are found naturally in the human body (the “microbiome”) influence a range of biological processes, including development, immunity, and nutrition. This effort will not only improve our understanding of how one biosystem (an individual's microbiome) relates to disease, but will also generate resources and support the development of new technologies and computational approaches—all crosscutting outputs that can be applied to investigations of other biosystems. Another new initiative at the biomedical research frontier is the NIH Roadmap Epigenomics Program, which will scan the human genome to study hereditable features that do not involve changes to the underlying DNA sequence, but significantly affect gene expression and are important for informing us about

how DNA is regulated. This global analysis of epigenetic changes should reveal new cellular pathways and mechanisms that influence disease progression.

The Common Fund also enables NIH to continue building research teams of the future; growing the Clinical and Translational Science Award Program; sustaining the transformation of the clinical research enterprise, in order to speed new discoveries from bench to bedside; investing strategically at the boundaries between the life and physical sciences, where so much transformative science, such as nanomedicine (the control of matter on the atomic and molecular scale), is taking place; and, through the Pioneer Award Program, nurturing bold ideas that, although they may have more than the usual degree of risk, if successful, will have unusually high scientific impact.

Nurturing a new generation of innovators is critical to our future research endeavors. NIH makes strategic investments at every level of the pipeline to improve the flow of talent drawn from every part and population of America. We produce teaching supplements that help educators from grades 2 through 12 convey difficult concepts through engaging activities, improving health literacy, and hopefully sparking children's interests in careers in research. We have programs that give undergraduate students research experiences, especially geared toward harvesting the vast potential of young people from groups that have been historically underrepresented in the sciences. NIH grants fund graduate students and postdoctoral fellows who go on to fill most every niche in the American biomedical research enterprise—from academic research to private industry, and from venture capitalists to policy makers. To support our new investigators and our most creative scientists, NIH recently established a series of new grants, including the “Pathway to Independence Award” and the “New Innovator Award.” Through these programs, nearly 200 of the most promising postdoctoral scientists will be chosen annually to receive 5-year bridging funds during their transition to research independence, while nearly 40 of the Nation's exceptionally creative scientists will be annually selected to receive 5 years of support while taking unconventional approaches to tackling our most vexing biomedical problems.

We are in an era of unprecedented scientific opportunity. In the past year alone, a deluge of genetic discoveries—the outcome of NIH's Human Genome and HapMap projects—promises to usher in a new epoch of biomedical research. To capitalize on recent research insights and technological advances, with partners from the various sectors of the Nation's health enterprise, NIH will build on past successes in basic, translational, and clinical research to keep America on the road to health through the new millennium. We need to sustain this momentum, as progress in the life sciences in this century will be a major determinant of our Nation's health, competitiveness, and standing in the world.

Elias A. Zerhouni, M.D.
Director, National Institutes of Health
January 15, 2008

Introduction

NIH Overview

The NIH mission is to uncover new knowledge that will lead to better health for everyone.

To many Americans, the names of one or more of the 27 ICs that comprise NIH may be more familiar than NIH as a whole. The name of an IC generally reflects its focus on a specific disease (e.g., cancer, diabetes), an organ system (e.g., heart, eye), life stage (e.g., children, the aging population), an overarching field of science (e.g., human genome, nursing), or a technology (e.g., biomedical imaging, information technology). It is the strength of each IC's expertise that provides the firm foundation enabling NIH to address the remarkable breadth and complexity of the biomedical and behavioral research it supports and conducts in the interest of improving public health. The ICs *support* research and training through extramural activities and most also *conduct* research and training through intramural activities. (See information below regarding the intramural and extramural research programs.)

The Office of the Director (OD), NIH, provides leadership, oversight, and coordination for the entire NIH research enterprise. The Division of Program Coordination, Planning and Strategic Initiatives, a new structure within the NIH OD, mandated by the NIH Reform Act of 2006, incorporates functions of the Office of Portfolio Analysis and Strategic Initiatives (which has primary responsibility for trans-NIH research initiatives based on NIH-wide portfolio assessment, strategic planning, evaluation, and assessment) and the research coordination functions of the four OD Program Offices. These OD program offices fund research using IC award-making authorities. Often, ICs partner with an office, supplementing its funding on a specific program or project.

Also within OD, many offices develop NIH policy and provide essential NIH-wide oversight and coordination in the areas of Science Policy, Science Education, Biotechnology Activities, Legislative Policy, Communications and Public Liaison, Ethics, Equal Opportunity and Diversity Management, Administrative Management, Budget, Financial Management, Human Resources, Research Services, Technology Transfer, Management Assessment, Management Planning, and Legal Counsel. The policies and activities of some of these offices are highlighted throughout the sections that follow as they relate to NIH research activities and policies. Also within OD are the Office of Extramural Research, which coordinates and oversees NIH policy on research supported by NIH and performed under grants and other award mechanisms by non-NIH institutions, and the Office of Intramural Research, which coordinates and oversees research conducted in NIH laboratories. These offices are discussed in some detail in the sections below.

Following is a list of NIH ICs and OD program offices linked to the home page on their Web sites. The ICs are presented in the order in which they appear on the appropriation table in the Congressional Justification. Appendix B provides brief descriptions of the missions of the ICs and OD program offices and live links to IC and office strategic plans. The mission statements and strategic plans provided by Appendix B classify and justify NIH priorities.

Institutes and Centers

- National Cancer Institute (NCI)
- National Heart, Lung, and Blood Institute (NHLBI)

- National Institute of Dental and Craniofacial Research (NIDCR)
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
- National Institute of Neurological Disorders and Stroke (NINDS)
- National Institute of Allergy and Infectious Diseases (NIAID)
- National Institute of General Medical Sciences (NIGMS)
- Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)
- National Eye Institute (NEI)
- National Institute of Environmental Health Sciences (NIEHS)
- National Institute on Aging (NIA).
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
- National Institute on Deafness and Other Communication Disorders (NIDCD)
- National Institute of Mental Health (NIMH)
- National Institute on Drug Abuse (NIDA)
- National Institute on Alcohol Abuse and Alcoholism (NIAAA)
- National Institute of Nursing Research (NINR)
- National Human Genome Research Institute (NHGRI)
- National Institute of Biomedical Imaging and Bioengineering (NIBIB)
- National Center for Research Resources (NCRR)
- National Center for Complementary and Alternative Medicine (NCCAM)
- National Center on Minority Health and Health Disparities (NCMHD)
- John E. Fogarty International Center (FIC)
- National Library of Medicine(NLM)
- NIH Clinical Center
- Center for Information Technology (CIT)
- Center for Scientific Review (CSR)

Office of the Director, Division of Program Coordination, Planning and Strategic Initiatives (DPCPSI)

- Office of Portfolio Analysis and Strategic Initiatives (OPASI)
- Office of Disease Prevention (ODP)
    - Office of Rare Diseases (ORD)
    - Office of Dietary Supplements (ODS)
    - Office of Medical Applications of Research (OMAR)
- Office of Behavioral and Social Sciences Research (OBSSR)
- Office of Research on Women's Health (ORWH) (ORWH)
- Office of AIDS Research (OAR)

Introduction
Extramural and Intramural Research Programs

Extramural Research Program

More than $8 of every $10 appropriated to NIH is awarded by the ICs through grants and contracts to the extramural community. The extramural community is composed of scientists at universities, medical centers, hospitals, and research institutions throughout the United States and abroad. The extramural research community comprises scientists and research personnel affiliated with over 3,100 organizations, including universities, medical schools, hospitals, and other research facilities located in all 50 States, the District of Columbia, Puerto Rico, Guam, the Virgin Islands, and points abroad. With NIH support, these investigators and their institutions conduct the vast majority of research that leads to improvements in the prevention, detection, diagnosis, and treatment of disease and disability; contributes to training the next generation of researchers; and enhances the skills and abilities of established investigators. The NIH OD Office of Extramural Research (OER) provides leadership, oversight, tools, and guidance to administer the NIH grants management operations carried out through the ICs. OER is where grants policy, program coordination, compliance, and electronic Research Administration (eRA) converge. The Deputy Director for Extramural Research executes program coordination through counterparts in each of the grant-awarding ICs.

NIH Peer Review Process

All grant applications and contract proposals for research funding undergo evaluation through peer review, in which external expert panels determine which applications or proposals are the most scientifically and technically meritorious and should be considered for funding. NIH policy requires that peer review be carried out in a manner that ensures objectivity, fairness, and maximum competition. The NIH dual (two-level) peer review system is mandated by the Public Health Service Act and Federal regulations (42 CFR 52).

CSR is the portal for NIH grant applications and their review for scientific merit. The NIH grant peer review process begins with assignment. Applications relevant to the NIH mission receive two types of assignment. One assignment is to a CSR Scientific Review Group (SRG) or, if the application is in response to a solicitation, to an IC special emphasis panel, for evaluation of scientific and technical merit. The second assignment is to an IC that has a mission encompassing the aims and objectives of the application. NIH uses established referral criteria (called Referral Guidelines) to determine the appropriate SRG to carry out review and the IC most suitable to potentially fund the project.

At the first level of review, peer reviewers evaluate and judge the overall scientific and technical merit of the research proposed in the application. SRGs conducting the first level of review are composed primarily of non-Federal researchers who are actively involved in the area of the proposed research and qualified to review the applications by virtue of their research experience and training. These peer reviewers are consultants to NIH and they provide advice about the potential of the research to advance scientific knowledge and discovery, using standardized criteria for determining the scientific and technical merit of an application, specifically:

1. **Significance**: Does the study address an important problem?
2. **Approach**: Are the concepts and methods well thought out and appropriate to the aim?
3. **Innovation**: Does the project develop or use novel concepts?

4. **Investigators**: Are the investigators appropriately trained and well suited to carry out the work?
5. **Environment:** Will the setting for the research (facilities, resources, institutional support) contribute to probability of success?

All of these criteria are necessary factors in determining the overall scientific and technical merit of an application and the final evaluation score or "priority score" of an application. Additional review criteria may be added for applications in response to solicitations (e.g., a Request for Applications, or RFA).

The second level of peer review is performed by the National Advisory Councils or Boards (Advisory Councils) of each IC, which are composed of scientific and nonscientific public members chosen for their expertise, interest, or activity in matters related to a specific area of health and disease. The vast majority of SRG-scored applications assigned to an IC go to the appropriate Council[1], which then recommends those applications that should be considered for funding. Identifying applications that further specific program priorities is a particularly important function of this second level of peer review. However, like SRGs, Advisory Councils recommend, but do not make, funding decisions.

An ongoing trans-NIH effort to examine the two-level NIH peer review system with the goal of optimizing its efficiency and effectiveness is discussed in *Enhancing Peer Review*, under the section below on *Improving Research Management.*

Funding Decisions

Only applications that are scientifically meritorious, based on SRG review, and favorably recommended by the National Advisory Council may be considered for funding. The priority score given to an application during the peer review process is important, but not the sole factor determining an IC's funding decision. Other considerations are programmatic relevance, IC priorities, contribution to balance in light of the existing IC research portfolio, and amount of the award.

Many ICs establish a "payline"—a percentile-based[2] funding cutoff point determined at the beginning of the fiscal year (FY) by balancing the projected number of applications coming to an IC with the amount of funds determined by NIH and the IC to be devoted to such projects. Because the significance of the proposed research is a critical factor in determining the priority score, applications that score within the payline are most likely to be funded. However, Advisory Councils consider, evaluate, and make recommendations on specific applications that score both within and beyond the payline.

In addition to setting paylines, many ICs establish procedures for funding applications that scored beyond the payline. Terms used for this category of awards vary by IC, but include "select pay," "exception pools," "high program-priority," and "special emphasis." What is consistent is the use of these funds, with strong justification, to support highly innovative or high program priority applications that score beyond the payline.

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[1] Councils do not receive unscored applications (these are applications deemed "not recommended for further consideration [NRFC]") at the first level of peer review. Also, until enactment of the NIH Reform Act of 2006, Councils were not obligated to review applications for less than $50,000. Moreover, of applications sent to Council, many IC Councils evaluate only those scoring over a prescribed threshold of success at the first level of peer review.

[2] Percentile represents the relative position or rank of each priority score (from 1 to 100).

Post-Award Administration

NIH policies extend into the post-award phase of research as well, so that NIH can monitor research progress and ensure responsible conduct of research. Scientific monitoring includes reviewing yearly progress reports, financial reports submitted by grantees, the publications generated by the research, and any invention reports. NIH also monitors compliance with Federal rules on protection of animals used in research and on human subjects (see *Ensuring Responsible Research Conduct* below). In addition, oversight of clinical research may involve data safety monitoring.

Oversight of initiatives involves another level review. NIH staff track what is funded under each initiative and may hold follow-up advisory group meetings, workshops, and/or formal program evaluations. This type of information becomes yet another source of input for the IC as it evaluates priorities and considers midcourse adjustments to initiatives and strategic plans.

Intramural Research Program

Approximately 10 percent of NIH funds support research activities carried out by NIH scientists in NIH laboratories on its campuses in the Bethesda (including the NIH Clinical Center), Rockville, Frederick, and Baltimore, Maryland, areas; Research Triangle Park, North Carolina; Phoenix, Arizona; and the Rocky Mountain Laboratories, Montana. The NIH Intramural Research Program, or IRP, conducts basic, translational, and clinical research. Most ICs have an intramural program; the exceptions are NIGMS, CSR, FIC, NCRR, and NCMHD[3]. Organizationally, the individual laboratories and clinics answer to their respective IC, and generally are responsible for conducting original research consonant with the goals of their IC. Approximately 1,150 principal investigators lead intramural research projects. The NIH Office of Intramural Research (OIR) is responsible for trans-NIH oversight and coordination of intramural research, human subjects' protections, animal welfare, training, policy development, laboratory safety, and technology transfer conducted within NIH laboratories and clinics. OIR is led by the NIH Deputy Director for Intramural Research and its oversight responsibilities are carried out in conjunction with the IC Scientific Directors. A summary of policies governing intramural research can be found in the *Intramural Research Sourcebook.*

As with the extramural program, intramural research proposals are generated by scientists. In the intramural research program, however, program directions and priorities are not generally shaped through grant awards[4], but rather through professional hiring and promotion decisions, external reviews, and the allocation of resources to laboratories and branches.

Each intramural research program has a promotion and tenure committee that evaluates all recommendations for professional appointment or promotion. In addition, there is a central tenure committee that reviews all candidates for tenure at the NIH. Through a competitive process, only approximately 60 percent of the individuals who enter the tenure track at the NIH, after a national search, eventually become permanent tenured staff.

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[3] Although NCMHD does not have an intramural program per se, some NCMHD funds are applied to intramural activities in partnership with other ICs.

[4] In July 2007, NIH issued NOT-RM-07-011 notifying members of the NIH IRP that Roadmap requests for allocations from the IRP will be considered on a competitive basis along with Roadmap applications from members of the extramural scientific community. CSR will be responsible for initial peer review involving competition among members of the IRP and the extramural scientific community.

Although tenure guarantees a base salary, research resources are competitive. Tenured and tenure-track scientists undergo formal, annual, internal reviews. Resource allocation and promotions are determined from these reviews. In addition, at least every 4 years, an external expert Board of Scientific Counselors (BSC) reviews the work of each tenured/tenure-track scientist and makes recommendations regarding continuation or modification of projects and adjustment of resources (budget, space, personnel). The IC Director or Scientific Director reports the results of BSC reviews to the IC National Advisory Council.

Each IC intramural research program is led by a Scientific Director. Scientific Directors are evaluated for performance by an external committee every 5 years. The reviewing committee reports to the IC National Advisory Council through the IC Director and to the NIH Deputy Director for Intramural Research.

Moreover, each IC intramural research program is reviewed in its entirety by a “blue ribbon” panel approximately every 10 years. These panels assess and make recommendations concerning the impact of the research program, program balance, and other significant matters that play a role in the success of the program.

Introduction
Strategic Planning and Roadmap 1.5

Strategic planning at NIH takes place at many levels. The U.S. Congress, through the NIH authorization and appropriations processes, sets IC funding levels, establishes the missions for some ICs, and directs NIH attention to particular areas of research interest or emphasis[5]. The Administration also establishes priorities for improving the health of the Nation that must be addressed by NIH. An example is Healthy People 2010[6], a comprehensive set of disease prevention and health promotion objectives for the Nation to achieve by 2010. Healthy People 2010 has two overarching goals—"Increase Quality and Years of Healthy Life" and "Eliminate Health Disparities"—and NIH is understandably the lead or co-lead for many of the specific topic areas. In addition, NIH establishes its goals and priorities fully cognizant of the framework of the *HHS Strategic Plan Goals and Objectives* - FY 2007-2012[7], which sets the stage for individual performance plans and outcome measures across NIH.

Some strategic plans pertain to the whole agency, for example, the NIH Roadmap for Medical Research. NIH initiated the Roadmap planning process in 2002 by consulting broadly with stakeholders to identify and prioritize the most pressing problems (roadblocks) facing medical research that could be uniquely addressed by NIH as a whole. Ideas for Roadmap initiatives were formulated from those initial consultations and then vetted based on whether the initiative had high potential to transform the way health research is conducted, would synergize with but cut across the individual missions of the ICs, would not be redundant with activities conducted by other agencies or entities, and be expected to have an impact on public health such that results should be broadly disseminated and in the public domain. This novel NIH-wide planning process launched a set of over 30 initiatives under three broad themes in 2003. The first set of Roadmap initiatives already is deepening our understanding of molecular biology and its role in health and disease; creating tools for 21st century biomedical research; stimulating interdisciplinary research teams; promoting high-risk breakthrough science; and reengineering the clinical research enterprise. NIH institutionalized this NIH-wide planning process when it established the Office of Portfolio Analysis and Strategic Initiatives (OPASI) in spring 2006. That summer, OPASI began soliciting ideas for the next generation of Roadmap initiatives. When NIH established OPASI, it also enhanced NIH's systems for gathering and analyzing information in support of strategic planning (see sections on *OPASI* and on *Roadmap* 1.5, below).

Although the Roadmap process is novel, NIH has a significant tradition of NIH-wide and trans-NIH strategic planning. The *NIH Strategic Research Plan and Budget to Reduce and Ultimately Eliminate Health Disparities* is a prominent example of an NIH-wide plan. Trans-NIH strategic plans focus on areas that are best addressed by involving multiple ICs in identifying research goals and priorities; for example, the Strategic Plan for NIH Obesity Research was developed by the NIH Obesity Research Task Force, led by NIDDK and NHLBI. The Plan seeks to maximize collaboration among the ICs and OD Offices to capitalize on their respective capabilities. Recent initiatives (FY 2006 and 2007) relate to translational research for the prevention and control of diabetes and obesity (NIDDK and OBSSR); bioengineering and obesity (NHLBI, NCI, NIA, NIBIB, and NIDDK); and identifying and reducing factors within health care systems that result in disparate health outcomes for patients with diabetes or obesity-related conditions (NIDDK), among others. Other trans-NIH research plans address goals and objectives in

[5] For more information, see http://officeofbudget.od.nih.gov/PDF/Significant%20Items-2008.pdf

[6] For more information, see http://www.healthypeople.gov/

[7] For more information, see http://www.hhs.gov/strategic_plan/

areas that include neuroscience research, HIV/AIDS, liver disease, diabetes, health disparities, muscular dystrophies, autoimmune diseases, and more.

Naturally, however, the majority of strategic planning at NIH is IC-based. IC strategic plans function as guideposts to the investigative and NIH communities. Each NIH IC has unique processes for developing and disseminating its strategic plans, but by developing and articulating consensus on today's most pressing health needs and research questions, all IC strategic plans influence the research directions and methods proposed by investigators in their applications. By the same token, strategic plans inform IC decisions about areas of research that require stimulation—achieved through a variety of means including meetings, workshops, conferences, Program Announcements, and Requests for Applications, and Requests for Proposals—to move science planning into the implementation stage. Finally, strategic plans influence IC decisions on which applications to fund.

While each of the 24 grant-making ICs has a broad Strategic Plan that clearly states its mission and priorities, many of the ICs also have disease- and program-specific strategic plans and research agendas as well as reports from workshops, “blue ribbon” panels, and other expert panels that contain recommendations for research goals or priorities within the IC mission.

Strategic planning at NIH is a highly consultative process involving many constituencies that generate and provide input on public health needs and research gaps, opportunities, and priorities. Importantly, strategic plans also serve as a means for ICs to measure and report on portfolio balance and progress relative to their missions. NIH stays constantly tuned to the twin touchstones for priority-setting-public health need and state of the science. In Chapter 2, at the end of each disease topic section, are lists of relevant strategic plans.

Division for Planning and Strategic Initiatives

As noted above, the NIH Reform Act of 2006, signed into law in January 2007, created the new Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) within the NIH/OD. The purpose of DPCPSI is to identify and report on research that represents important areas of emerging scientific opportunity, rising public health challenges, or knowledge gaps that deserve special emphasis and would benefit from the conduct or support of additional trans-NIH research (research that involves collaboration between two or more ICs), or would otherwise benefit from strategic coordination and planning. As specified in the NIH Reform Act of 2006, a Council of Councils, which met for the first time in November 2007, advises the NIH Director on matters related to the policies and activities of DPCPSI. To a large extent, the legislative mandate for DPCPSI confirms the administrative action that NIH took when it established OPASI. As such, OPASI will continue its role in developing and managing Roadmap initiatives as an integral part of DPCPSI.

Office of Portfolio Analysis and Strategic Initiatives

When NIH established OPASI in spring 2006, the aim went beyond institutionalizing the Roadmap planning and investment process. OPASI's full role is to provide NIH and the ICs with the methods and information necessary to manage their large and complex scientific portfolios; to lead trans-NIH efforts in identifying new and shifting public health challenges and important areas of emerging scientific opportunity; and to assist in accelerating trans-NIH investments in these areas, focusing on those involving multiple ICs.

OPASI develops and employs databases, analytic tools, and methodologies to conduct key assessments and portfolio analyses and integrates these analyses with information from multiple other sources for use in identifying and recommending concepts for trans-NIH initiatives. Since evaluation is an integral part of strategic planning and priority-setting, OPASI also is responsible for planning, coordinating, and conducting program and initiative evaluations. As part of its evaluation agenda, OPASI subjects each Roadmap initiative to rigorous review, with

outcome tracking, an annual review of progress, and a major review not later than the fourth year of the initiative. In addition, OPASI is responsible for overseeing and coordinating IC use of evaluation set-aside funds and the systematic assessments required by the Government Performance and Results Act (Pub. L. No. 103-62) and application of the OMB Program Assessment Rating Tool.

Roadmap 1.5 and the Common Fund Strategic Initiative Process

Roadmap initiatives are a collective NIH-wide resource supported through the NIH Common Fund. They were previously funded through IC and OD contributions, but since FY 2007 have been funded within the OD appropriation level. While OPASI does not have direct grant-making authority, the Common Fund provides an "incubator space" for Roadmap and other initiatives on a time-limited basis (5 to 10 years). Initiatives either transition out to the ICs after this 5- or 10-year period or are concluded. In this way, NIH can remain nimble in responding to newly identified emerging research needs that have the potential to transform biomedical or behavioral research.

To perpetuate the Roadmap, OPASI manages the process by which recommendations for trans-NIH strategic initiatives are selected and developed, and provides the information needed for NIH leadership to allocate resources effectively for these trans-NIH efforts.

Criteria for Major Roadmap Initiatives

- Is the proposed initiative truly transforming—could it dramatically affect how biomedical and/or behavioral research is conducted over the next decade?
- Will the outcomes from the proposed initiatives synergistically promote and advance the individual missions of the ICs to benefit health?
- Does the proposed initiative require participation from NIH as a whole and/or does it address an area(s) of science that does not clearly fall within the mission of any one IC or OD program office?
- Is the proposed initiative something that no other entity is likely or able to do, and is there a public health benefit to having the results of the research in the public domain?

The process is exemplified by the steps OPASI took in 2006 and early 2007 to select and plan the next generation of Roadmap initiatives—Roadmap 1.5—which will be funded in FY 2008.

Through summer and fall 2006, NIH solicited ideas for new initiatives from the intramural and extramural scientific community, patient advocates, and the general public to help senior NIH staff identify crosscutting challenges in biomedical research that meet special criteria established for Common Fund (Roadmap) initiatives. One of the important steps in this process was issuance of a Request for Information published in the NIH Guide[8] in October 2006. The respondents were invited to submit up to three ideas that met predetermined criteria to be considered for a Roadmap initiative.

[8] For more information, see http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-011.html

To facilitate the prioritization of ideas, OPASI coordinated a programmatic review of the submitted ideas assessing their responsiveness to the criteria. To further inform the decision-making process, OPASI and ICs worked together to provide a preliminary assessment of the currently funded portfolio of research related to several of the broad areas highlighted by the ideas. OPASI efforts to develop portfolio analysis tools will enhance NIH capacity for these analyses. Informed by this analysis and following extensive scientific discussion, the IC Directors selected broad areas that were to be pursued either as major Roadmap initiatives, pilot studies, coordination areas, or strategic planning areas.

Next, Trans-NIH Working Groups, led by IC Directors, developed specific proposals in the identified broad areas. Then, in May, the IC Directors and NIH Director met to review and prioritize the proposals. They selected two topics, the Microbiome and Epigenetics, for immediate implementation as 5-year Major Roadmap Initiatives. Although the Reform Act was not enacted in time for NIH to establish and convene the Council of Councils during consideration of concepts for Roadmap 1.5, in the future the Council will act as an external advisory panel to the IC Directors during the concept approval stage of Roadmap initiatives.

- ***Microbiome***. The Microbiome is the full collection of microbes (e.g., bacteria, fungi, viruses) that naturally exist within and on the human body. In a healthy adult, microbial cells are estimated to outnumber human cells by a factor of 10 to 1. These communities, however, remain largely unstudied, leaving almost entirely unknown their influence on human development, physiology, immunity, and nutrition. The NIH Human Microbiome Project (HMP) will generate the tools and resources necessary for comprehensive characterization of the human microbiota and analysis of their relationship to human health and disease.
- ***Epigenetics/Epigenomics***. Epigenetics is the study of changes in gene expression or function that are caused by factors other than change in DNA sequence. Epigenetic changes allow cells to have different characteristics despite containing the same genomic material. Curiously, some epigenetic features are inherited from one generation to the next. This subject is of such current scientific interest that the prominent journal Cell recently devoted an entire special review issue to the subject [9]. The overall hypothesis of the NIH Epigenomics Program is that the origins of health and susceptibility to disease are, in part, the result of epigenetic regulation of the genetic blueprint. Initiatives in this area would develop a "toolbox" to better measure these genetic modifications; collect data and develop algorithms to build the infrastructure needed to model epigenetic processes; and incorporate epigenetic information in genetic studies to increase our understanding of the relationship to human health and disease.

Other topics were approved as pilot studies, coordination areas, and strategic planning areas (see Appendix C, the *Common Fund Strategic Planning Report, FY 2008*, for further information on plans for use of the Common Fund).

[9] *Cell*, 128, February 23, 2007.

Introduction
Other Crosscutting Activities and Policies

Chapters 2 and 3 of this Report summarize NIH research activities on the topics specified in the statute mandating this report. Chapter 2 summarizes research activities on topics that are disease-specific (e.g., those regarding cancer and chronic diseases). Chapter 3 summarizes activities from the perspective of key research approaches and resources (e.g., genomics, clinical and translational research, research training, and health communications). Other activities essential to the mission of the NIH—technology transfer, science education, providing a platform for discovery, improving the management of research, and ensuring responsible research and development—are summarized below.

Technology Transfer and Sharing

Federal and NIH policy requires that the outcomes of NIH research be made available to the public. Provisions of the Bayh-Dole Act (35 U.S.C. 200 et seq.) and the Federal Technology Transfer Act (15 U.S.C. 1501 et seq.) are intended to stimulate the commercialization of federally funded inventions by ensuring the transfer of federally funded technology to the private sector.

The NIH Office of Technology Transfer (OTT) develops technology transfer policies that are approved by the PHS Technology Transfer Board. Technology transfer and sharing policies, as they apply to extramural research, are developed with and administered by OER. These policies include principles, guidelines, and regulations related to publication, invention reporting, and intellectual property policy matters. OER policies are designed to enhance access to publications resulting from NIH-funded research; ensure appropriate sharing of data, tools, and research resources; and promote the transfer of technology (in the form of licenses and patents). All recipients of Federal grants or contracts must report details of inventions and patents that have been made through such awards. NIH developed an online Extramural Invention Information Management System (Edison) in 1995 for Bayh-Dole reporting compliance, and now administers the Interagency Edison system (iEdison) through which inventions supported by any of 18 Federal research agencies can be reported.

Intramural policies and activities are managed by the Office of Technology Transfer (OTT) in the NIH OIR. As mandated by the Federal Technology Transfer Act and related legislation, OTT evaluates, protects, licenses, monitors, and manages the wide range of intramural NIH and U.S. Food and Drug Administration (FDA) discoveries, inventions, and other intellectual property. A large part of OTT's responsibility for technology transfer is carried out by retaining title to inventions developed in NIH and FDA laboratories and licensing these inventions to the private sector entity best suited to conduct the further research and development needed for potential commercialization and public health benefit. The NIH Pipeline to Partnerships (P2P) searchable database is a new resource developed to encourage the development of technologies licensed from OTT or being developed by NIH SBIR/STTR awardees by showcasing them for an audience of potential strategic partners, investors, and licensees. The P2P database provides an additional avenue by which NIH can facilitate more rapid development of products for the benefit of public health.

Science Education and Literacy

NIH takes an active role in science education and science literacy activities. These activities aim to attract young people to biomedical and behavioral science careers, lay the groundwork for advanced study, enhance public understanding of health science, and empower the public as consumers of science and health information.

Curriculum supplements —ready–to–use, interactive teaching units—are one of NIH's most popular and effective science education efforts. Crafted through a unique partnering of NIH scientists, teachers, and expert curriculum developers, the supplements are aligned with State education standards and are consistent with the National Science Education Standards. NIH has shipped nearly 300,000 curriculum supplements to K-12 educators across the Nation. Topics covered include "The Science of Healthy Behaviors," "Cell Biology and Cancer," "Sleep, Sleep Disorders, and Biological Rhythms," and "The Brain: Understanding Neurobiology through the Study of Addiction."

NIH aims to engage students and the public in the wonders of biology and biomedical research through other thought-provoking programs as well. For those who are interested in a career in the life sciences, NIH provides resources such as LifeWorks®, a career exploration Web site for middle and high school students, their parents, teachers, and career guidance counselors. Lifeworks® includes in-depth career information on more than 100 health and medical science-related careers. Users can search the site and generate a customized list of careers that match their skills and interests. "SciLife" is an annual health and biomedical career planning workshop for parents and high school students. NIH also sponsors a speakers' bureau that provides engaging science professionals to talk to school groups and local and national organizations.

NIH's Science Education Partnership Awards (SEPA) funds innovative educational programs, such as collaborations among biomedical and clinical researchers and teachers and schools, museums and science centers, media experts, and other educational organizations that generate educational resources such as curricula; exhibits; films; student, teacher, and parent workshops; after-school and summer hands-on science programs; essay contests; and science fairs. A dedicated SEPA Web site provides access to the educational materials and expertise produced through these efforts. SEPA enables researchers, educators, and community groups to share their knowledge, expertise, and enthusiasm about health and science research with K-12 students and the general public.

Providing the Platform for Discovery

Buildings and Facilities

With more than 18,000 employees and 229 government-owned buildings in six locations, the facilities infrastructure maintained by the OD Office of Research Facilities is the literal foundation for a successful research program. The facilities necessary to support 21st century science are far more sophisticated than yesterday's bricks, mortar, pipes, and lines. From biosafety to facilitating team science, the requirements of today's research create greater demands in providing and sustaining a safe, healthy, and functional environment for employees and patients.

The Clinical Center

The Clinical Center is the Nation's largest hospital devoted entirely to research. Here, NIH scientists work to translate laboratory discoveries into better means to improve the Nation's health. Comprising two facilities—the Mark O. Hatfield Clinical Research Center, which opened in 2005, and the original Warren Grant Magnuson Clinical Center, which opened in 1953—the Center houses inpatient and outpatient units as well as research laboratories and features a unique design that locates patient care units in close proximity to cutting-edge laboratories doing related research. This facilitates interaction and collaboration among clinicians and researchers. More than 1,600 intramural NIH laboratories use the Center to conduct research. The Center has more than 100,000 outpatient visits a year and 7,000 inpatient admissions. Approximately 1,200 credentialed physicians, dentists, Ph.D. researchers, 660 nurses, and 570 allied health care professionals such as pharmacists, dietitians, and medical technologists work at the Center. As a research facility, only patients with the precise kind or stage of illness under investigation are admitted for treatment under a protocol, but subjects who are enrolled in clinical studies receive

the benefit of access to cutting-edge technologies and compassionate care.

The Library

Through the National Library of Medicine (NLM), NIH provides the world's largest medical library. The Library collects materials in all areas of biomedicine and health care. The collections stand at more than 9 million items—books, journals, technical reports, manuscripts, microfilms, photographs, and other images. Housed within the Library is one of the world's finest medical history collections of old and rare medical works. Far more than a physical facility, the Library is responsible for MEDLINE®, a database freely accessible on the Internet through PubMed®, which has more than 16 million journal article references and abstracts going back to the mid-1960s with another 1.5 million references back to the early 1950s. Some 900 million searches of MEDLINE are done each year by health professionals, scientists, librarians, and the public. Links from references to full text articles increasingly are available.

To maintain the currency of its collection, the Library selects, orders, and acquires publications from a wide variety of sources. Each year NLM receives, reviews, and processes approximately 25,000 monographic items for possible addition to the NLM collections, and acquires, licenses, and processes over 22,000 print, non-print, and electronic serial titles.

To manage its collection and maximize accessibility, the Library employs sophisticated cataloging and indexing schemes that in and of themselves are important tools for the Nation's network of medical libraries. These activities include maintaining and developing the online NLM Classification, a scheme for the shelf arrangement of medical literature in libraries, and MeSH, the Library's controlled vocabulary thesaurus. MeSH consists of sets of terms naming descriptors in a hierarchical structure that permits searching at various levels of specificity. The MeSH thesaurus is used for indexing articles from 4,800 of the world's leading biomedical journals for the MEDLINE/PubMED® database. It also is used for the NLM-produced database that includes cataloging of books, documents, and audiovisuals acquired by the Library. Each bibliographic reference is associated with a set of MeSH terms that describe the content of the item. Similarly, search queries use MeSH vocabulary to find items on a desired topic.

Information Technology

Information technology (IT) and computational science increasingly are essential to deciphering the complexity of biological systems. The NIH Center for Information Technology (CIT) provides core IT infrastructure, system security, and services ranging from cable and server acquisition and management, to video conferencing and Web site development, as well as providing the policy framework for IT activities undertaken by other ICs. In addition, CIT and many ICs provide NIH scientists with access to the sophisticated systems, analytic tools, and databases necessary to advance quantitative investigations in fields such as molecular biology and proteomics (for additional information see the section on Disease Registries, Databases, and Biomedical Information Systems in Chapter 3). From supercomputing to management of an Image Processing Facility, CIT also provides the NIH intramural community with invaluable scientific support tools and resources.

Public-Private Partnerships

The NIH Program on Public-Private Partnerships was established in 2006 within the NIH Office of Science Policy as a Roadmap initiative to facilitate collaborations to improve public health through biomedical research. As the central NIH resource on public-private partnerships, the program provides guidance and advice to NIH and potential partners on the formation of collaborations that leverage NIH and non-NIH resources to achieve synergy. NIH partnerships can be established directly between NIH (as a whole or through one or more ICs) and any of a wide range of other organizations, including patient advocacy groups, foundations, pharmaceutical or

biotechnology companies, academic institutions, and the Foundation for the NIH (FNIH), an independent, private charitable foundation established by Congress. The Program works with the ICs and OD Offices to review existing partnership mechanisms and recommend policies or legal authorities needed to achieve NIH objectives and manage intellectual property, achieve data access and sharing, and address human subjects protections and other concerns. In September 2007, the Program issued, in the NIH *Manual*, a reference guide to many of the relevant legal authorities, policies, ethics issues, and other considerations in using the various available mechanisms to create public-private partnerships.

Improving Research Management

Enhancing Peer Review

In June 2007, NIH embarked on a trans-NIH effort to examine the two-level NIH peer review system with the goal of optimizing its efficiency and effectiveness, while ensuring that NIH continues to meet the needs of the research community and public at large. The examination involves leaders from across the scientific community through two working groups—one external and one internal. Both groups are seeking broad input. Information collection efforts included a Request for Information published in the *NIH Guide* seeking comments and creative concrete suggestions on how to enhance the system; an internal NIH staff survey; regional meetings around the country; and consultations with professional societies and advocacy groups. After all of the input has been analyzed, both working groups will meet in January 2008 to develop a set of integrated recommendations for next steps.

In parallel with NIH's examination of the peer review system, CSR launched several peer review pilots and initiatives that will inform this ongoing effort. Based on a two-stage pilot test that began early in 2006, NIH shortened the review cycle for new investigators submitting R01 applications. (The R01 is the most common mechanism of grant support for individual investigators.) Before the pilot, on average, it took 10.3 months from the receipt of an application until NIH made an award to support the proposed research. For new applicants, CSR now posts the conclusions of peer review meetings within 10 days. This acceleration gives new applicants opportunity to revise and resubmit amended applications for the next review cycle—4 months sooner than the previous opportunity for resubmission. Since new investigators, by definition, have had no previous R01 support, any delay in their ability to submit an amended application could have a negative impact on their careers. NIH has great interest in the career development of new scientists and this initiative is just one example of NIH's commitment to supporting new investigators in their efforts to obtain R01 research grant funding. NIH is now working toward shortening the review cycle for all applicants.

CSR also has been developing and testing different modes of conducting peer review to enhance the recruitment of the best reviewers. One experiment involves scheduling some study section meetings in areas outside the Washington, D.C., area so meeting sites and travel are more convenient for reviewers.

New Investigators

New investigators are the innovators of the future—they bring fresh ideas and technologies to bear on biomedical and behavioral research problems and they pioneer new areas of investigation. Entry of new investigators into the ranks of NIH-funded researchers is essential to the health of this country's research enterprise. Because of that, NIH interest in the training and funding of new investigators is deep and longstanding. NIH exceeded its target of 1,500 new investigators attaining project grant support in FY 2007. In addition, NIH established two new programs to help new investigators in their quest to become independent research scientists—the Pathway to Independence Award and NIH Director's New Innovator Award. The Pathway to Independence Program, announced in January 2006, offers a new opportunity for promising postdoctoral scientists to receive both mentored and independent research support from the same award. This new award mechanism is a bridge that will accelerate the transition of

new, creative scientists from research dependence to research independence. The NIH Director's New Innovator Award, announced in March 2007 as a component of the NIH Roadmap, supports exceptionally creative scientists who take highly innovative, even unconventional, approaches to major challenges in biomedical or behavioral research. New Innovator Awards are reserved for investigators who have not yet received a regular research (R01) or similar grant.

Aligning Grant Applications with Team Science

In February 2006, NIH announced a pilot initiative to alter a longstanding policy and allow more than one principal investigator (PI) on a grant application. This multiple-PI model enables investigators to share the authority, responsibility, and credit for leading and directing a project—intellectually and logistically—and encourages collaboration among equals, when a "team science" approach is the most appropriate way to address a scientific problem. This policy change began as a 2005 Roadmap initiative to stimulate interdisciplinary science. In 2006, NIH and the White House Office of Science and Technology Policy solicited advice and comments on this topic from the scientific community. On the basis of the NIH pilot and received advice, all Federal research agencies are preparing to formally implement policies and procedures allowing multiple PIs on research awards. NIH released its implementation guidance to the community in November 2006 and most electronic applications were modified to accept multiple PIs beginning with January receipt dates in 2007. On June 25, 2007, NIH released a Federal Register Notice of Proposed Rule Making to solicit input on the change in definition to accommodate multiple PIs. A notice addressing those comments is being prepared.

Streamlining Grant Management

NIH constantly strives to make the process of receiving and reviewing grants more efficient. To understand the importance of this streamlining, consider the fact that NIH receives nearly 80,000 applications per year. Moving from a paper-based to an electronic submission process is central to the streamlining effort. NIH recently passed the mark at which over 75 percent of all grant applications are submitted electronically, via the Web portal of Grants.gov. Simultaneously, NIH is phasing out the Public Health Service grant application form and replacing it with a federal-wide application. This represents a significant reduction in burden for applicants who otherwise have to contend with a variety of forms and information requirements depending on the agency to which they apply. The advent of electronic receipt of grant applications has improved the clarity of application materials delivered to reviewers. It also will enable the use of artificial intelligence software to automate referral to NIH Institutes and review committees. The expanded use of Internet Assisted Review allows reviewers to electronically submit critiques and initial priority scores before review meetings as a means of streamlining the review as well as shortening review meetings. These changes will make the review process more effective and less onerous and eventually will lead to a reduction in the time from receipt to award.

The "NIH Guide for Grants and Contracts" is NIH's primary means of communication with the extramural community. The "Guide" publicizes policy changes, research solicitations, and other notices. Because many funding announcements are trans-NIH solicitations, drafting announcements can involve considerable collaboration. NIH is in the process of developing an Automated Guide System to serve as a document/content management system in support of the "Guide" publication process. This solution will supplant the current manual process of collaboration and review that goes into publishing funding announcements. The management system will facilitate communications and the exchange of data between and among ICs and within the Office of the Director. It also will provide a more efficient and cost-effective means of publishing NIH funding opportunity announcements. A pilot of the system was launched during summer 2007 and a final application will be released in spring 2008.

A first-ever NIH Division of Extramural Activities Support (DEAS) started operations in October 2004. This new organization—the largest A-76 activity at NIH—provides support services for grants management, peer review, and

scientific program management functions. The reorganization of extramural support services into DEAS represents a major change in NIH business practices, from a decentralized operation to a centrally managed unit using standardized operating procedures. Experience with the new organization demonstrated that improvements are needed in its efficiency and effectiveness to best meet IC needs. NIH reengineered the organization to better align staff skills with required responsibilities, be more cost-effective, enable DEAS staff to achieve career growth, and foster better working relationships between DEAS and its IC customers. A new organizational structure was implemented in September 2007.

Ensuring Responsible Research

NIH is committed to promoting scientific progress in a transparent and responsible manner. Several OD offices have, or share, responsibility for the development and implementation of policies and procedures to ensure that research is conducted safely, ethically, and securely.

Biotechnology Activities

The Office of Biotechnology Activities (OBA) within the OD Office of Science Policy continually monitors scientific research and progress in the areas of recombinant DNA and genetics technologies in order to anticipate future developments, including potential ethical, legal, and social concerns. In accord with these responsibilities, OBA manages the operation of, and provides analytical support to, the NIH Recombinant DNA Advisory Committee (RAC) and the HHS Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS). OBA also manages the National Science Advisory Board for Biosecurity, which is addressed in Chapter 2 in the section on *Infectious Diseases and Biodefense*, and the NIH/FDA Genetic Modification Clinical Research Information System (GeMCRIS), a comprehensive information resource and analytical tool for scientists, research subjects, sponsors, institutional oversight committees, Federal officials, and others with an interest in human gene transfer research.

RAC reviews all proposals for human, gene-transfer clinical research (often referred to as “gene therapy”) at institutions receiving NIH funds for recombinant DNA research. RAC review occurs before biosafety review at the institution where the research will be conducted. This enables RAC review to inform local review. As a Federal advisory committee, RAC issues recommendations to the NIH Director. RAC proceedings and reports are posted to the OBA Web site to enhance their accessibility to the scientific and lay publics. As new issues are identified, RAC helps NIH develop safety symposia and policy conferences to engage the scientific and public communities in thoughtful dialogue regarding emerging issues and concerns. RAC has been a vital national forum promoting critically important scientific progress in a transparent, responsible, and safe manner and enhancing public trust in the science.

SACGHS provides policy advice to the Secretary, HHS, on the broad array of complex medical, ethical, legal, and social issues raised by the development and use of genetic technologies. In 2006, SACGHS began an in-depth fact-finding process on the U.S. system of oversight of genetic testing. The Secretary's charge for this inquiry is to undertake the development of a comprehensive map of the steps needed for evidence development and oversight for genetic and genomic tests, with improvement of health quality as the primary goal. In November 2007, SACGHS issued a draft report for public comment.

Human Subjects Protections in Research

The HHS Office for Human Research Protections (OHRP) implements the Federal regulations governing the protection of human subjects 45 CFR 46 for all HHS agencies, including NIH. OHRP is responsible for (1) negotiating assurances with each institution that conducts HHS-sponsored human subjects research, (2) registering local Institutional Review Boards (IRBs), which assess risk, benefit, and many other matters with respect to proposed and ongoing studies involving human subjects, (3) issuing policy and guidance that clarifies the regulations, and (4)

providing educational materials and programs for investigators and IRBs, and overseeing compliance. Because of the clinical research conducted in the NIH intramural program, NIH itself has an assurance with OHRP.

Although 45 CFR 46 is called the "Common Rule" and some 17 Federal agencies, including the National Science Foundation, Department of Defense, and Department of Veterans Affairs are governed by the rule, implementation policies vary and parallel regulations, e.g., for FDA, compound the differences in agency human subject protection practices. In fact, variability exists even across NIH ICs.Recognizing that this variability can hamper the efficiency and effectiveness of the clinical research system (because it requires the research community to understand and fulfill multiple requirements that may be redundant or even conflicting), NIH created a Clinical Research Policy Analysis and Coordination (CRpac) Program to serve as a focal point for harmonizing, streamlining, and optimizing human subjects protection policies and requirements. Launched as an NIH Roadmap initiative, CRpac aims to develop clear, effective, and coordinated rules for clinical research to achieve maximally effective human subjects protections. High on CRpac's list of problems to tackle is the variation in requirements for reporting adverse events. (An adverse event is an unfavorable medical occurrence associated with the subject's participation in the research). Investigators and IRBs face multiple requirements regarding the content, format, and timing of adverse event reports that must be made to different agencies and oversight bodies. Working closely with the preexisting Federal Adverse Event Task Force (FAET), CRpac gathered and analyzed adverse event terms, definitions, and rules contained in a wide array of regulations, policies, and guidance documents across many agencies; documented the workflow for reviewing and using adverse event information; and developed a draft Basal Adverse Event Report (BAER)—a single core report that PIs could send to multiple agencies for consideration. In addition, CRpac formed a Trans-NIH Adverse Event Steering Committee to analyze NIH-specific needs and requirements for adverse event information and proposeways to coordinate and streamline the reporting policies of the ICs. In addition, to launch a dialogue on the characteristics nd relative benefits of various models of IRB review, in November 2006, CRpac helped sponsor a National Conference on Alternative IRB Models.

The Office of Human Subjects Research in the NIH OIR manages human subject protection activities in the intramural program. Functioning under the assurance NIH filed with OHRP, and in cooperation with the ICs, the Office implements NIH policy, establishes and maintains the 14 NIH IRBs, and provides training for researchers and IRB members. In addition, the Office manages the Human Subjects Research Advisory Committee, which advises the Deputy Director for Intramural Research—who is the Institutional Official responsible for human subjects investigations at NIH—on policies and procedures regarding the conduct of human subject research.

Within the NIH Clinical Center, the site of most NIH intramural human subjects research, the Department of Bioethics provides a center for research, training, and service related to bioethical issues. The Department conducts conceptual, empirical, and policy-related research into bioethical issues; offers comprehensive training and educational programs in bioethics; provides ethics consultation services to clinicians, patients, and families; and is available as a source of advice to the NIH IRBs.

Animal Care and Use in Research

The Office of Laboratory Animal Welfare (OLAW) in the Office of Extramural Research (OER) oversees the use of animals in Public Health Service (PHS)-supported biomedical and behavioral research. OLAW provides guidance and interpretation of the *PHS Policy on Humane Care and Use of Laboratory Animals* (PHS Policy), monitors compliance with the PHS Policy, and supports educational programs that further the humane care and use of research animal subjects. As a condition of receiving PHS support for research involving laboratory animals, institutions must provide a written Animal Welfare Assurance (Assurance) to OLAW describing in detail the means they will use to comply with the PHS Policy and Federal statutes and regulations relating to animals. OLAW

negotiates and approves these Assurances as required by HHS acquisition regulations and the PHS Policy. The assurance commits the institution and its personnel to full compliance with the PHS policy. OLAW holds accountable and depends upon institutional officials, Institutional Animal Care and Use Committees, research investigators, and other agents of the institution to ensure conformance with the institution's Assurance. This includes evaluating all allegations or indications of noncompliance with Federal animal welfare requirements.

OLAW maintains a comprehensive Web site with links to relevant laws, policies and guidance, an online tutorial, and a variety of other training materials and resources regarding laboratory animal welfare. In 2006, when OLAW published "What Investigators Need to Know About the Use of Animals," it added a significant new brochure to the materials it offers. Humane care and use of animal subjects in biomedical and behavioral research is monitored by several Federal agencies and regulated by numerous guidelines and regulations. The brochure provides a complete, concise overview of all the regulations that apply to PHS-funded investigators. Response to the brochure from the research community has been overwhelmingly positive and OLAW has distributed more than 60,000 copies.

A new source of information on the need for animals in research is in development by NIH[10]. Animals in Research will be a Web-based resource for the public, grantee investigators and institutions, and NIH staff. The OER Web site will provide information on the critical role of this research for improving human and animal health, the latest breakthroughs in animal-based research, new funding opportunities, up-to-the-minute policy and training information, and guidelines for grantee institutions' emergency preparedness and crisis communication.

The Office of Animal Care and Use (OACU) in the NIH OIR administers the intramural program of animal care and use. OACU develops guidelines and policies for the responsible care of laboratory animals and the proper operation of NIH animal facilities and offers a variety of training courses and health and safety information for personnel who work with animals. Each NIH component that uses animals in research has an Animal Care and Use Committee that reviews and approves requests to use animals in research. In addition, each component's animal care and use program is directed by a senior veterinarian. An Animal Research Advisory Committee meets monthly to discuss trans-NIH topics and provide advice to the NIH Deputy Director for Intramural Research, who is the NIH institutional official accountable for animal care and use. All components of the intramural NIH animal care and use program are accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International.

Ethical Conduct

The fundamental Federal principles of ethical conduct hold that conscientious performance of duty is placed above private gain, that employees shall not have financial interests that conflict with that duty, and that employees will avoid any actions creating the appearance that they are violating the law or the standards of ethical conduct. It is the responsibility of every NIH employee to abide by the statutes and regulations, including the supplemental standards of ethical conduct for HHS employees, and the implementation policies and procedures of NIH. Significant ethics training resources at NIH help employees to meet that responsibility. The NIH Ethics Program consists of a central NIH Ethics Office located organizationally within the NIH OD and an ethics office in each IC, managed by a Deputy Ethics Counselor and an Ethics Coordinator. Attorneys from the HHS Office of the General Counsel, Ethics Division, maintain an office at NIH to provide legal advice and assist IC ethics counselors and coordinators as needed.

[10] When the Animals in Research Web site goes live in June 2008, the URL will be: http://grants.nih.gov/grants/policy/air/index.htm

The Ethics in Government Act (5 U.S.C. App.) requires each agency to provide an initial ethics orientation to new employees. NIH provides a Web-based training system for completing this requirement and the mandatory annual training. Also, NIH ethics staff is readily available to answer questions and provide ethics and conflict-of-interest counsel, as needed, and the central Ethics Office provides extensive information and resources on its Web site.

Prudent stewardship of public funds requires that appropriate steps be taken to ensure objectivity in research and freedom from financial conflicts of interest. Therefore, each institution receiving NIH research funds must have written guidelines on the avoidance of conflicts of interest. These guidelines must cover financial interests, gifts, gratuities and favors, nepotism, and other areas such as political participation and bribery. They also must indicate how outside activities, relationships, and financial interests are reviewed by the responsible and objective institution official(s). Institutions that identify research investigator financial conflicts are required to report the conflicts to the NIH Grants Management Officer at the funding IC.

The most recent edition of the "Guidelines for the Conduct of Research (2007)" sets forth the general principles governing the conduct of good science as practiced in the NIH IRP, including the responsibilities of research staff in the collection and recording of data, publication practices, authorship determination, mentoring, peer review, confidentiality of information, collaborations, human subjects research, financial conflicts of interest, and animal care and use.

NIH also has established conflict of interest, confidentiality and nondisclosure rules for reviewers of grant applications and R&D contract proposals. The rules require reviewers to identify and certify real or apparent conflicts of interest both pre- and post-meeting. Employment, financial benefit, personal relationships, professional relationships, or other interests may be a basis for a conflict of interest, and any one condition may serve to disqualify a reviewer from participating in the review of an application or proposal.

Conflicts of interest are especially problematic in clinical research. For that reason, the HHS Office for Human Research Protections issued specific guidance on "Financial Relationships and Interests in Research Involving Human Subjects." Moreover, in February 2007, NIH updated its "Guide to Preventing Financial and Non-Financial Conflicts of Interest in Human Subjects Research at NIH." "The Guide," directed at the intramural community, aims to ensure both the integrity of research and the safety of subjects in the intramural program.